To perform mononuclear cell phenotyping, 20 μl of well-mixed MultiTEST four-color reagent (CD3/CD8/CD45/CD4) (Becton Dickinson Biosciences, San Jose, CA) and 50-μl aliquots of EDTA-anticoagulated whole blood were added to a TruCOUNT tube (Becton Dickinson Biosciences, San Jose, CA) containing a known concentration of beads. The mixture was incubated for 20 min at room temperature in the dark before 450 μl of FACS lysing solution (Becton Dickinson Biosciences, San Jose, CA) was added. After 15 min of incubation, the lyse/no-wash-stained samples were analyzed with the FACSort flow cytometer (Becton Dickinson Immunocytometry Systems, San Jose, CA). Data were analyzed using MultiSET software (Becton Dickinson Immunocytometry Systems, San Jose, CA).

Contact enrollments

Contacts of SFV-infected participants were evaluated annually for evidence of SFV infection by WB testing of serum or plasma and PCR testing of PBMC DNA, but are not interviewed.

RESULTS

Primary participants

Seven of 13 persons eligible to participate enrolled for long-term follow-up. We refer to these participants as cases 2, 3, 6, 7, 9, 10, and 12 to be consistent with previous reports and the chronological order in which they were identified as SFV-infected.[10,12] Sequence analysis indicates that the virus infecting cases 2 and 3 originated from baboons while virus infecting the remaining five participants all originated from chimpanzees.[10,12] Case 11 dropped out of the initial surveillance study and was not available for further study.[10]

Table 1 summarizes demographic and exposure data of SFV-infected persons by enrollment status. Participants are not entirely representative of the eligible population, limiting interpretation of results. Male gender, higher level job status, and longer duration of both occupational exposure and SFV serpositivity are overrepresented among study participants.

All participants are male compared to four/six (67%) eligible persons who did not enroll ("nonparticipants"). Two of five (40%) animal caretakers, both animal care supervisors, the sole research associate, and two/four (50%) veterinarians participated. At the time SFV infection was confirmed, the median age of participants (median 56, range 41–62 years) was similar to that of three nonparticipants for whom age was available (median 57, range 49–58). Participants enrolled a median of 2 years (range 1–5) after infection was confirmed. Participants were exposed to NHPs longer prior to confirmation of infection than were five nonparticipants for whom adequate data were available (median 26, range 8–37 years versus median 19, range 10–29 years, respectively).

The availability of stored serum allowed determination of a minimal duration of seropositivity for six/seven participants and four/six nonparticipants. Prior to documentation of SFV infection,

TABLE 1. DEMOGRAPHIC AND EXPOSURE CHARACTERISTICS OF ELIGIBLE AND ENROLLED PARTICIPANTS

Case	Sex[a]	SFV species origin	Occupation	Age when SFV infection documented (years)	Year SFV infection documented	Year first positive sera archived	Minimal duration (years) SFV infection when identified	Duration of NHP exposure (years) when SFV infection identified
				Enrolled participants				
2	M	Baboon	Research associate	56	1996	1978	18	29
3	M	Baboon	Animal care supervisor	57	1996	1988	8	37
6	M	Chimpanzee	Veterinarian	60	1998	1981	17	19
7	M	Chimpanzee	Veterinarian	41	1999	1990	9	23
9	M	Chimpanzee	Animal caretaker	41	1999	1980	19	8
10	M	Chimpanzee	Animal care supervisor	50	1999	1976	23	26
12	M	Chimpanzee	Animal caretaker	62	2001	NA[b]	NA	32
				Eligible nonparticipants				
1	M	AGM[c]	Animal caretaker	57	1996	1995	1	19
4	M	Baboon	Veterinarian	49	1997	1994	3	20
5	M	Baboon	Veterinarian	58	1998	1979	19	29
8	M	Chimpanzee	Animal caretaker	NA	1999	1985	14	>14
13	F[d]	Chimpanzee	Veterinary technician	NA	2002	NA	NA	11
14	F	Chimpanzee	Animal caretaker	NA	2002	NA	NA	10
				Ineligible nonparticipants				
11	M	Chimpanzee-like[d]	Research technician	NA	1999	NA	NA	10

[a]M, male; F, female.
[b]NA, not available.
[c]AGM, African green monkey.
[d]Based on SFV-type-specific WB.

participants with available stored sera were seropositive a median 9 years longer than were nonparticipants (median 17.5, range 8–23 years versus median 8.5, range 1–19 years, respectively). Initial clinical testing of participants under this protocol occurred after a median of 19 years (range 2–24) of documented infection.

Exposure history and use of protective equipment

All seven participants reported direct, frequent, and intimate opportunity for exposure to NHPs and their biological fluids including animal saliva, urine, feces, and blood. All seven workers reported histories of both mucocutaneous exposures to NHP body fluids and skin-penetrating injuries. Five of seven participants (71%) described NHP bite wounds, five/seven (71%) described scratch wounds, and six/seven (86%) described percutaneous exposure to NHP body fluids via skin penetrating sharp injuries. However, only four/seven (57%) participants (cases 3, 6, 7, and 9) described a percutaneous injury that was associated with the NHP species from which sequence analysis suggests their infecting virus arose.

All participants reported currently wearing leather or latex gloves when handling NHPs. However, these seven participants worked with NHPs for a median of 16 years (range 5–29) prior to 1988 when universal precaution guidelines were established. Five workers consistently and two inconsistently wore gloves prior to 1988. All reported historically inconsistent use of face shields and goggles transitioning to more regular use in recent years. Two participants denied use of goggles or face shields for mucocutaneous protection; four reported wearing them 25–75% of the time for specific tasks such as working with chemicals or infected animals or cleaning cages. One wore face shields consistently "when required." The use of protective equipment was rare prior to 1988, and workers noted that current use of face shields did not always protect them from mucocutaneous exposure to NHP saliva and other body fluids.

Body distribution of SFV

The distribution of SFV in human body fluids is summarized in Table 2. SFV DNA sequences were found in PBMCs from all seven persons and in all of their 19 serial samples tested. Virus culture was attempted at least once on PBMCs from six/seven participants. SFV was isolated from only one/two PBMC samples from each of cases 6 and 10, representing 33% of persons and 20% of specimens from which virus culture was attempted.

SFV DNA was detected in oral cavity specimens from three/seven (43%) participants; overall, 6/16 (38%) throat swab samples from these seven participants were SFV DNA positive. Saliva specimens from two/seven (29%) persons were positive for SFV DNA; 6/23 (26%) serial samples were positive. Interestingly, SFV was isolated from throat swab samples from case 6, for whom six/seven (86%) oral cavity specimens were positive for SFV DNA. SFV was not isolated from saliva available from the other five participants (seven samples).

Although all subjects provided urine specimens, most (13/18, 72%) samples had insufficient cellular DNA present to support SFV PCR testing. Of five samples from four persons with sufficient cellular DNA, two persons (cases 3 and 6) were positive for SFV DNA. Two participants (cases 2 and 12) each provided two semen samples; a third (case 6) provided a single specimen. Specimens from case 2 (who had received a vasectomy more than 20 years ago) and case 12 tested negative for B-actin sequences, indicating the absence of cellular DNA or the presence of PCR inhibitors. Thus these semen specimens were not suitable for further PCR testing. The semen specimen from case 6, who had benign hemospermia, was positive for SFV DNA. Insufficient material was available to attempt virus isolation from semen or urine specimens.

SFV-specific immunoglobulin G (IgG) antibodies against structural (Gag) and accessory (Bet) proteins were detected by WB in plasma, saliva, and urine from participants. Immunoglobulin A antibodies were not detected in any specimens, as previously reported.[19]

Clinical status

Self-reported medical histories identified chronic conditions, nonspecific symptoms, and diseases of aging common in the U.S. population. In addition, case 9 reported congenital heart disease and mild thrombocytopenia since 1997 and case 3 underwent aortic valve replacement during this observational pe-

TABLE 2. PRESENCE OF SFV IN BODY COMPARTMENTS

	Number of specimens positive/number of specimens tested (%)					
	Peripheral blood mononuclear cells		*Oral cavity*[a]		*Urine*[b]	*Semen*[b]
Enrollee	*SFV DNA (%)*	*SFV isolation (%)*	*SFV DNA (%)*	*SFV isolation (%)*	*SFV DNA (%)*	*SFV DNA (%)*
Case 2	2/2 (100)	0/1 (0)	0/6 (0)	0/2 (0)	0/1 (0)	NT[c]
Case 3	4/4 (100)	0/2 (0)	0/4 (0)	0/4 (0)	1/1 (100)	NT
Case 6	4/4 (100)	1/2 (50)	6/7 (86)	1/4 (25)	1/2 (50)	1/1 (100)
Case 7	4/4 (100)	0/2 (0)	0/9 (0)	0/4 (0)	0/1 (0)	NT
Case 9	1/1 (100)	0/1 (0)	1/2 (50)	0/2 (0)	NT[c]	NT
Case 10	3/3 (100)	1/2 (50)	0/6 (0)	0/2 (0)	NT	NT
Case 12	1/1 (100)	NT	3/5 (60)	NT	NT	NT
Total	19/19 (100)	2/10 (20)	10/39 (26)	1/18 (6)	2/5 (40)	1/1 (100)

[a]Includes throat and saliva swabs and parotid saliva.
[b]Specimen quantity insufficient for SFV isolation.
[c]NT, not tested.

riod. No symptom or diagnostic patterns suggested a common clinical syndrome associated with SFV infection.

Results of clinical laboratory testing for each participant are summarized in Table 3. Repeated clinical laboratory testing was within normal limits for cases 2, 10, and 12. Testing identified unremarkable patterns of mildly abnormal glucose and renal function tests compatible with a three decade history of diabetes (case 3) and of fluctuating mild liver transaminase elevations (case 7).

Clinical laboratory testing identified hematological abnormalities for three participants. Three times on annual testing case 6 had eosinophil counts at the lower limit of or below normal range; his eosinophil count was within normal limits on subsequent testing in May 2002. Mild thrombocytopenia without other blood count abnormalities was confirmed in case 9. In addition to mild laboratory abnormalities expected to accompany long standing diabetes, case 3 had the unexpected findings of intermittent mild thrombocytopenia accompanied by natural killer (NK) cell lymphocytosis (NKCL). NK cells [$CD3^{-}CD16^{+}56^{+}$ cells] at three time points were 44% (780/μl), 39% (854/μl), and 38% (840/μl), respectively (upper normal limit 25% or 480/μl). Additional hematological tests performed by a specialized laboratory on specimens collected 9 months apart (personal communication, W.G. Morice, II and A. Tefferi, Mayo Clinic) repeatedly showed that 40% of lymphocytes were CD16-positive, CD3-negative NK cells, expressing CD56 and CD57, and CD161 with partial loss of CD94. These findings along with other tested markers indicated monoclonal NKCL consistent with a chronic NK-large granular lymphocytosis (indolent large granular lymphocytosis) of unclear clinical significance. The patient has no related clinical symptoms.

Secondary transmission

Wives of cases 2, 3, and 9 were tested for SFV infections as contact participants. All remained WB and PCR negative despite a collective minimum of 57 person-years of intimate exposure to an SFV-infected partner (median 20, range 13–24 years). The wives of three additional nonparticipants also tested SFV negative.[10,12] All participants reported intimate marriages that provided frequent opportunity for exposure to saliva and other body fluids. All denied the routine use of barrier precautions or other practices documented to minimize sexual transmission of infections.

Case 2 ceased regular blood donation in 1969. A serum collected in 1967 was WB negative; the next available specimen collected in 1978 was WB seroreactive. Cases 6, 7, and 10 ceased regular blood donation when notified of SFV infection; retrospective testing of archived sera confirmed earlier seropositivity. As previously reported elsewhere, four recipients of leuko-reduced blood products from one SFVcpz-infected donor (case 6) showed no evidence of SFV infection.[20]

DISCUSSION

This is the first longitudinal description of the clinical, immunological, and virological status of humans infected with SFV. After a minimum median of 26 years (range 6–31) of documented infection as of 2007, participants continue to demonstrate strong antibody response by WB testing. Viral DNA can be consistently detected in all subjects' PBMCs but inconsistently from other body sites. SFV was successfully cultured from the throat swab and PBMCs of one participant and from the PBMCs of a second. SFV DNA was also detected in the urogenital tract of two persons. Despite this, no secondary transmission among humans via intimate exposure or blood product transfusion from one SFV-infected donor was identified.[20] Our data support a persistent infection in humans consistent with the demonstrated nature of endemic infections in NHPs, but suggest that the presence of detectable viral DNA in human body fluids does not correlate with transmissibility.

Repeated exposure to SFV DNA in body fluids may be insufficient for human-to-human transmission due to a limited viral load, the persistent presence of virus in a latent noninfectious state, or other mechanisms. SFV isolations were most frequent from case 6, the only participant whose specimens were received and processed within 8 h of collection. This may suggest that time elapsed from collection to processing influenced virus recovery, or may reflect higher viral loads in case 6 than other participants. Quantitative PCR testing for viral DNA and RNA levels in blood and other body compartments might provide further insight on the relationship between variations in viral load and inconsistencies between detection of SFV DNA in, and isolation of SFV from, body fluids. Fluctuations in viral load may also explain the variable detection of SFV in some body fluids.

Six of seven retrovirus genera are associated with hematological, neurological, dermatological, arthritic, or oncogenic diseases affecting nearly all vertebrate species, typically after long incubation periods.[3] Despite being highly cytopathic in cell culture, FVs have not been associated with any *in vivo* disease.[6] Our preliminary observations on humans with prolonged infection, while limited, are reassuring. Most clinical laboratory results were within normal limits or explained by the presence of conditions common in human populations of comparable age.

The most intriguing clinical observations were mild hematological abnormalities in three participants. The fluctuating, inconsistent and mild eosinopenia of case 6 appears to be clinically insignificant. The mild thrombocytopenia in two/seven participants deserves attention, but also does not appear to be clinically significant.

Although the total lymphocyte counts in all participants were normal, the NKCL in one participant with minimal thrombocytopenia is a notable finding. NKCL is a rare condition of unknown etiology, accompanied by thrombocytopenia in 12% of subjects in one series.[21] Persistent viral infection (e.g., Epstein–Barr, hepatitis B or C viruses)[22] or persistent immunological stimulation[23] has been hypothesized to play an etiological role. With the caveat that we do not know whether case 3 has other persistent infections, we may speculate that persistent SFV infection and, possibly, the presence of long-term diabetes mellitus[24] might contribute to case 3's NKCL. Future studies quantifying SFV integration in specific blood cells or cell lines may cast light on whether SFV plays a role in the observed hematological abnormalities.

SFV transmits naturally among NHPs via casual exposure to oral and respiratory secretions, and has been experimentally

Table 3. Abnormal Clinical Laboratory Test Results over the Period of Follow-Up

Participant	*Years of age, Year 1*	*Known duration of infection (years), Year 1*	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
Case 2	62	23	WNL[a]	WNL	WNL	NA[b]	NA
Case 3	62	13	Glucose 111 mg/dl (65–109)[c]; creatinine 1.7 mg/dl (0.5–1.4); BUN[d] 33 mg/dl (7–25); NK[e] cells 780/μl, 44% (68–482, 4–25%)	NK cells 854/μl, 39%; uric acid 8.6 (1.7–8.2); platelets 138,000 (140,000–400,000)	Glucose 131 mg/dl; creatinine 1.4; ALT[f] 116 U/liter (5–35); NK cells 38%	NA	NA
Case 6	62	19	Eosinophils 34/mcl (50–500)	Eosinophils 17/mcl	Eosinophils 56; platelets 122,000	Eosinophils 33 (15–500)	WNL
Case 7	42	10	AST[g] 48 IU (0–42); ALT 70 IU (0–48)	ALT 67	WNL	NA	WNL
Case 9	41	20	Platelets 107,000	NA	NA	NA	NA
Case 10	50	24	WNL	WNL	WNL	NA	NA
Case 12	62	2	WNL	NA	NA	NA	NA

[a]WNL, within normal limits.
[b]NA, not available.
[c]Limits of normal are shown in parentheses.
[d]BUN, blood urea nitrogen.
[e]NK, natural killer.
[f]ALT, alanine aminotransferase.
[g]AST, aspartate aminotransferase.

transmitted among NHP through fresh whole blood.[5,6,25,26] Previous reports have stressed the role of skin penetrating injuries in human acquisition of infection.[10–12] The absence of a discernible history of percutaneous injury associated with the species from which the infecting virus strain arose for 43% of participants raises the possibility that human infection with SFV may be acquired through mucocutaneous exposure to SFV-containing NHP body fluids without injury, similar to the routes of transmission of simian herpes viruses.[27] Thus, it is prudent for persons occupationally exposed to NHPs to take precautions to avoid exposure to primate saliva and other body fluids through either percutaneous injuries or mucocutaneous exposures.

Limited observations have not identified infection-associated pathology or secondary SFV transmission among humans through either intimate contact or transfusion of blood products. However, the small number of observed individuals and the limited duration of follow-up restrict our ability to draw definitive conclusions about the clinical significance of human infection with SFV and the ability of SFV to transmit secondarily. Like HTLV, the incidence of disease may be low or may follow long latency periods. It is also unknown what effect, if any, immunosuppression may have on clinical outcomes of human infection with SFV. For example, SFV replication was recently shown to expand to the small intestinal jejunum of SIV-immunosuppressed macaques, a site for significant $CD4^+$ T cell depletion and inflammation in these animals, suggesting that SFV may play a role in the gut-associated pathology observed during progression to simian AIDS.[28] We caution SFV-infected persons to refrain from donation of biological materials for transfusion or transplantation pending a better understanding of the significance of human infection.[12,29] Additional observations will be necessary to further define the public health significance of zoonotic SFV infection.

ACKNOWLEDGMENTS

We are grateful to the study participants and to the biosafety officers who supported their enrollment and participation. We also thank William G. Morice II, M.D., Ph.D. and Ayalew Tefferi, M.D. at the Mayo Clinic for confirmation of a monoclonal NKCL consistent with a chronic NK-large granular lymphocytosis (indolent large granular lymphocytosis) in case 3.

Use of trade names is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services, the Public Health Service, or the Centers for Disease Control and Prevention. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

No authors have commercial or other associations that might pose conflicts of interest. All aspects of work reported in this paper were financed by the Centers for Disease Control and Prevention.

Portions of the work presented in this manuscript were previously presented as oral presentations at the 4th International Conference on Foamy Viruses, March 14–16, 2002, Atlanta, GA; the 9th Conference on Retroviruses and Opportunistic Infections, February 24–28, 2002, Seattle, WA; the International Conference on Emerging Infectious Diseases, March 11–14, 2002, Atlanta, GA; and the 11th International Conference on Human Retrovirology: HTLV and Related Viruses, June 9–12, 2003, San Francisco, CA.

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別紙様式第2-1

No. 10

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. 11. 25	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	Centers for Disease Control and Prevention (CDC). Morb Mortal Wkly Rep. 2007 Nov 16;56(45):1181-4.	公表国	
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）				米国	

研究報告の概要

○アデノウイルス血清型14に関連した米国4州の急性呼吸器疾患（2006～2007年の報告）

アデノウイルス血清型14型(Ad14)は、希にしか報告されないが新興しているアデノウイルスの血清型株で、健常若年成人を含め全ての年齢層の患者に、重症で時に致死性の呼吸器疾患を惹起する可能性がある。2006年5月に、ニューヨーク州で生後12日目の乳児が、Ad14が原因の呼吸器疾患により死亡した。2007年3月～6月の間に、オレゴン州、ワシントン州の介護施設、およびテキサス州の空軍基地で発生した小集積事例において、合計で140名のAd14感染患者が確認された。このうち53名(38%)が入院し、24名(17%)はICUで治療を受け、9名(5%)が死亡した。全4州の患者から分離されたAd14株は、hexonおよびfiber遺伝子全長の塩基配列データは同一であったが、1955年以来のAd14レファレンス株とは区別された。このことから、米国で新たなAd14変異株が新興し感染拡大したことが示唆される。州および各地公衆衛生当局は、Ad14が原因の集団感染発生可能性に警戒すべきである。

アデノウイルスは1950年代に初めて記録され、結膜炎、発熱性上気道疾患、肺炎および胃腸疾患などの広範囲な臨床症状に関連している。新生児や高齢患者、基礎疾患のある患者では重症化の可能性があるが、健常成人では一般的に致死性感染とはならない。本報告は、米国内に感染拡大した新規病原性Ad14変異株の新興を示唆している点で異例である。Ad14感染は1955年に初めて記録され、1969年にはヨーロッパの新兵での流行性急性呼吸器疾患と関連したが、それ以降はあまり検出されていなかった。Ad14のより広域での感染循環は数年前から発生している可能性もある。

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
2006～2007年に、米国ニューヨーク州、オレゴン州、ワシントン州、テキサス州で合計140名のアデノウイルス血清型14感染患者が確認され、新たなAd14変異株が新興し感染拡大した可能性が示唆されるとの報告である。	日本赤十字社は、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国（入国）後4週間は献血不適としている。また、問診で呼吸器疾患などの体調不良者を献血不可としている。今後も引き続き情報の収集に努める。

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