2004), and those subclassified previously (Saruwatari et al., 2002b; Takasaka et al., 2004) were all subjected to a phylogenetic analysis. Furthermore, we performed a single nucleotide polymorphism (SNP) analysis of 275 reported partial SC DNA sequences worldwide. Our results provide the basis for a discussion of ancient human dispersals carrying SC subgroups.

Materials and Methods

Geographic origins of JCPyV isolates

Using molecular cloning (see below), eight JCPyV isolates (UR-8, Han-1, -3 and -4, RH-2 and -5, and MU-4 and -7) were recovered in the current study, and seven isolates (C1, CW-7 and -11, ID-2, ML-2 and -4, and ZA-3) were obtained in a previous study (Guo et al., 1996), using urine samples collected from indigenous volunteers or patients aged 40 years or older at the sites indicated in Table 1 and Figure 1. The origins of the JCPyV isolates used in this study whose complete JCPyV sequences have been reported previously are also shown in Table 1 and Figure 1.

DNA Analysis

Full length JCPyV DNAs were cloned into pUC19 at the unique *Bam*HI site, as described previously (Yogo et al., 1991). The resultant complete JCPyV DNA clones were prepared using a QIAGEN Plasmid Mini kit (QIAGEN GmbH, Hilden, Germany). Purified plasmids were used in a cycle sequencing reaction using the DYEnamic ET Terminator Cycle Sequencing Kit (Amersham Biosciences, Buckinghamshire, England). The primers used were a set reported previously (Agostini et al., 1997), excluding JIG-9, JIG-10, JIG-53, and SEC-11, and four additional primers: W-11 (5′-AGTTTTTGAGGGAACAGAGGAG-3′), corresponding to nucleotides (nt) 283 to 310 in the JCPyV (Mad-1) genome (Frisque et al., 1984); W-1a (5′-CTTCGCCAGCTGT-CACGTAAGGCTTCTG-3′), corresponding to nt 283 to 310; and the M13 universal forward and reverse primers. DNA sequencing was performed using an automated sequencer (ABI PRISM 373S DNA sequencer, Applied Biosystems, Foster City, CA, USA).

Phylogenetic analysis

The non-coding control region of the JCPyV genome was excluded from the phylogenetic analysis since this region is hypervariable, especially in JCPyV isolates derived from the brain and the cerebrospinal fluid of PML patients (Yogo and Sugimoto, 2001) [One isolate, SA21_01, was recovered from the cerebrospinal fluid of a PML patient (Venter et al., 2004)]. DNA sequences were aligned using CLUSTAL W (Thompson et al., 1994) with a gap-opening penalty of 15.00 and a gap-extension penalty of 6.66. To evaluate the phylogenetic relationships among DNA sequences, the neighbor-joining (NJ) method (Saitou and Nei, 1987) in the CLUSTAL W program was used. Divergences were estimated using Kimura's two-parameter method (Kimura, 1980). To assess the confidence of branching patterns of the NJ tree, bootstrap probabilities (BPs) were estimated with 1000 bootstrap replicates (Felsenstein, 1985) using CLUSTAL W. The phylogenetic tree was visualized using

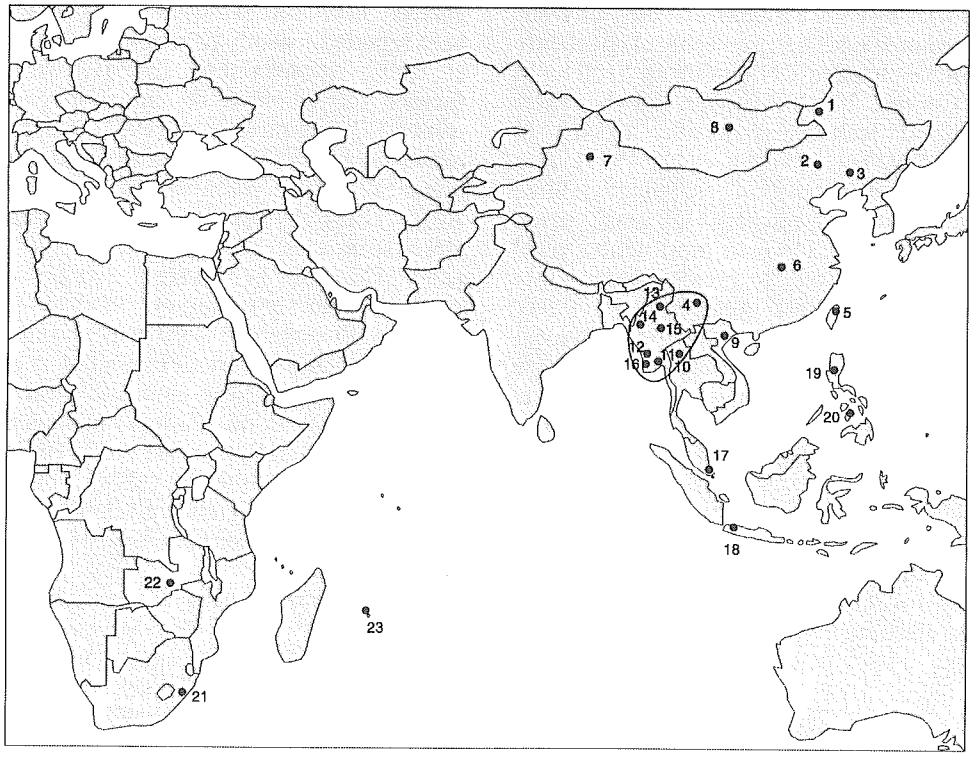

Figure 1. Sites of sample collection. Dots indicate the sites where samples were collected, and the numbers beside the dots indicate the site numbers (see Table 1). One site (Hawaii, site no. 24) is not shown. The region in which non-SC-f isolates were frequently detected is circled.

Table 1. Origin of JCV isolates whose complete DNA sequences were used in the phylogenetic analysis

Geographic origin (site no.[1])	Subgroup[2]	Isolates	5-bp deletion[3]	Accession no.[4]	Ref.[5]	
					R1	R2
Manzhouli, China (1)	SC-f	714A	+	AF300964	A	A
Chifeng, China (2)	SC-f	711A	+	AF300961	A	A
Chifeng, China (2)	SC-f	713A	+	AF300963	A	A
Shenyang, China (3)	SC-f	715A	+	AF300965	A	A
Kunming, China (4)	SC-f	710A	+	AF300960	A	A
Kunming, China (4)	SC-f	712A	+	AF300962	A	A
Kunming, China (4)	SC-a	716A	–	AF300966	A	A
Taipei, China (5)	SC-f	C1	+	AB198940	B	—
Taipei, China (5)	SC-f	C3	+	AB077873	B	C
Wuhan, China (6)	SC-f	CW-2	+	AB048579	B	G
Wuhan, China (6)	SC-f	CW-7	+	AB198942	B	—
Wuhan, China (6)	SC-f	CW-10	+	AB077872	B	E
Wuhan, China (6)	SC-f	CW-11	+	AB198943	B	—
Urumqi, China (7)	SC-f	UR-8	+	AB198941	—	—
Ulaanbaatar, Mongolia (8)	SC-b	MO-11	–	AB048582	B	G
Hanoi, Vietnam (9)	SC-f	Han-1	+	AB198944	—	—
Hanoi, Vietnam (9)	SC-f	Han-3	+	AB198945	—	—
Hanoi, Vietnam (9)	SC-f	Han-4	+	AB198946	—	—
Chiang Mai, Thailand (10)	SC-a	TL-2	–	AB077855	C	C
Chiang Mai, Thailand (10)	SC-a	TL-5	–	AB077856	C	C
Chiang Mai, Thailand (10)	SC-c	TL-7	–	AB077858	C	C
Yangon, Myanmar (11)	SC-f	MN-3	+	AB077879	C	C
Yangon, Myanmar (11)	SC-d	MN-6	–	AB077866	C	C
Yangon, Myanmar (11)	SC-d	MN-7	–	AB077867	C	C
Yangon, Myanmar (11)	SC-e	MN-11	–	AB077871	C	C
Rakhine, Myanmar (12)	SC*	RH-2	–	AB198947	—	—
Rakhine, Myanmar (12)	SC-f	RH-5	+	AB198948	—	—
Myitkyina, Myanmar (13)	SC-c	MT-1	–	AB077859	C	C
Myitkyina, Myanmar (13)	SC-c	MT-2	–	AB077860	C	C
Myitkyina, Myanmar (13)	SC-f	MT-10	+	AB077874	C	C
Myitkyina, Myanmar (13)	SC-f	MT-14	+	AB077861	C	C
Myitkyina, Myanmar (13)	SC-f	MT-15	+	AB077857	C	C
Myitkyina, Myanmar (13)	SC-e	MT-22	–	AB077868	C	C
Tiddim, Myanmar (14)	SC-d	TD-4	–	AB077862	C	C
Tiddim, Myanmar (14)	SC-d	TD-6	–	AB077863	C	C
Tiddim, Myanmar (14)	SC-d	TD-15	–	AB077864	C	C
Tiddim, Myanmar (14)	SC-d	TD-19	–	AB077865	C	C
Peinnebeen, Myanmar (15)	SC-f	PB-3	+	AB077876	C	C
Peinnebeen, Myanmar (15)	SC-f	PB-4	+	AB077877	C	C
Peinnebeen, Myanmar (15)	SC-f	PB-5	+	AB077878	C	C
Chaungtha Beach, Myanmar (16)	SC-e	CH-2	–	AB077869	C	C
Chaungtha Beach, Myanmar (16)	SC-f	CH-7	+	AB077875	C	C
Chaungtha Beach, Myanmar (16)	SC-f	CH-17	+	AB077870	C	C
Masai, Malaysia (17)	SC-f	ML-2	+	AB198950	B	—
Masai, Malaysia (17)	SC-f	ML-4	+	AB198951	B	—
Masai, Malaysia (17)	SC-f	ML-6	+	AB048581	B	G
Jakarta, Indonesia (18)	SC-f	ID-1	+	AB048580	B	G
Jakarta, Indonesia (18)	SC-f	ID-2	+	AB198949	B	—
Luzon, Philippines (19)	SC-f	Luz-1	+	AB113125	D	D
Luzon, Philippines (19)	SC-f	Luz-2	+	AB113132	D	D
Luzon, Philippines (19)	SC-f	Luz-3	+	AB113134	D	D
Luzon, Philippines (19)	SC-x	Luz-18	–	AB113130	D	D
Luzon, Philippines (19)	SC-x	Luz-19	–	AB113131	D	D
Luzon, Philippines (19)	SC-x	Luz-20	–	AB113133	D	D
Cebu, Philippines (20)	SC-f	Ceb-1	+	AB113118	D	D
Cebu, Philippines (20)	SC-f	Ceb-2	+	AB113122	D	D
Cebu, Philippines (20)	SC-f	Ceb-4	+	AB113123	D	D
Cebu, Philippines (20)	SC-x	Ceb-14	–	AB113119	D	D
Cebu, Philippines (20)	SC-x	Ceb-15	–	AB113120	D	D
Cebu, Philippines (20)	SC-x	Ceb-16	–	AB113121	D	D
Kwazulu-Natal, South Africa (21)	SC-f	SA21_01	+	AY536239	E	E
Lusaka, Zambia (22)	SC-f	ZA-3	+	AB198952	B	—
Port Louis, Mauritius (23)	SC-f	MU-4	+	AB198953	—	—
Port Louis, Mauritius (23)	SC-f	MU-7	+	AB198954	—	—

Table 1. (continued)

Geographic origin (site no.[1])	Subgroup[2]	Isolates	5-bp deletion[3]	Accession no.[4]	Ref.[5] R1	Ref.[5] R2
Hawaii, USA (24)	SC-x	732A	–	AF396427	F	F

[1] Indicated in Figure 1.
[2] Determined based on the phylogenetic analysis (Figure 2).
[3] Presence (+) or absence (–) of the pentanucleotide deletion spanning nucleotides nt 218 to 222. These nucleotide numbers are those of the archetype (Yogo et al., 1990) in the transcriptional control region.
[4] GenBank/EMBL/DDBJ accession numbers.
[5] R1, references for isolates; R2; references for sequences. A, Cui et al. (2004); B, Guo et al. (1996); C, Saruwatari et al. (2002b); D, Takasaka et al. (2004); E, Venter et al. (2004); F, Yanagihara et al. (2002); G, Sugimoto et al. (2002); —, this study.

the TREEVIEW program (Page, 1996).

Results

Phylogenetic analysis of SC isolates worldwide based on complete viral DNA sequences

We sequenced 15 complete JCV (SC) DNA clones, including seven established previously (Guo et al., 1996) and eight established in this study (the origins of these clones are shown in Table 1 and Figure 1). An NJ phylogenetic tree was constructed from these sequences and 50 complete SC sequences reported previously (Table 1). Thus, in this study, we subclassified 11 SC isolates in China, three in Vietnam, two in Malaysia, two in Myanmar, one in Indonesia, two in Mauritius, one in Zambia, one in South Africa, and one in Hawaii, USA.

According to the phylogenetic tree (Figure 2), the SC isolates worldwide can be classified into several clusters, previously designated SC-a to -f and SC-x (Saruwatari et al., 2002b; Takasaka et al., 2004), with BPs ranging from 46% to 100%. Although the BP for SC-f was not high (63%), we found that all SC-f isolates examined carried a unique pentanucleotide deletion in the transcriptional control region (Saruwatari et al., 2002b), whereas this deletion was absent in all other subgroups (Table 1).

It should be noted that six (710A to 715A) of the seven Chinese Type-7A isolates detected by Cui et al. (2004) were classified as SC-f, while one (716A) fell into the SC-a cluster (Figure 2). Furthermore, the Hawaiian isolate (732A) previously described as belonging to Type 7A (Yanagihara et al., 2002) was classified as SC-x, and the South African isolate (SA21_01) previously described as belonging to type 7 (Venter et al., 2004) was classified as SC-f (Figure 2).

The number of isolates belonging to each SC subgroup is shown for each country in Table 2, and the findings are summarized as follows: the SC-a to -e subgroups mainly contained isolates localized to an area including Myanmar, Thailand, and southwestern China; the SC-f subgroup contained isolates spread across all of China, southeastern Asia, and southern Africa; and the SC-x subgroup contained those localized to the Philippines and a single Hawaiian isolate. These results suggest that although SC isolates worldwide can be classified into several subgroups, only one (SC-f) has attained a worldwide distribution.

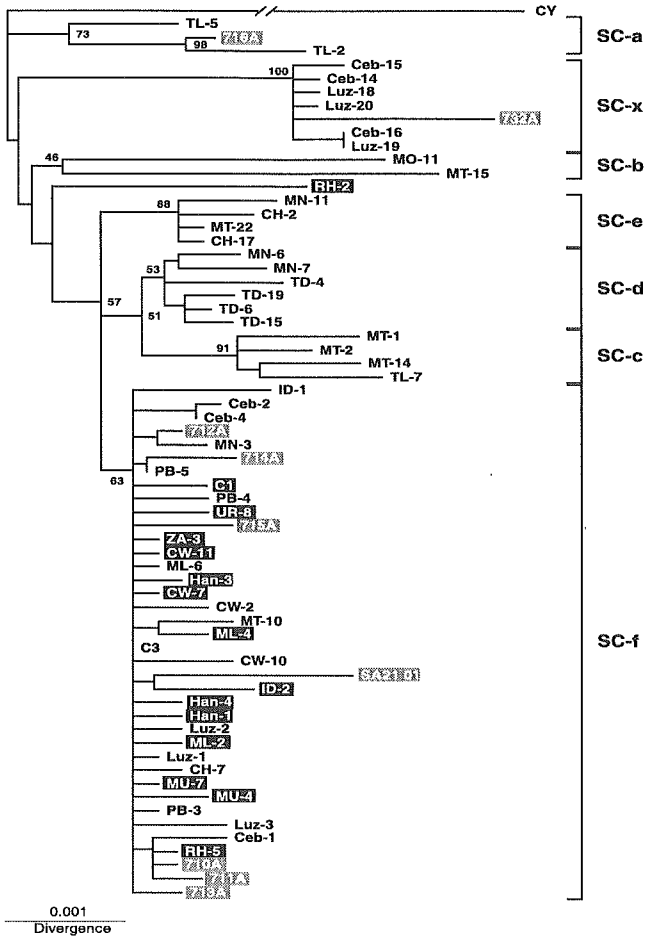

Figure 2. NJ phylogenetic tree relating 65 complete JCV (SC) DNA sequences. The phylogenetic tree was constructed from complete sequences, excluding regulatory sequences, using the NJ method. The phylogenetic tree was visualized using the TREEVIEW program. The tree was rooted using isolate CY as the outgroup, since this is a distinct genotype that is closely related to SC (Sugimoto et al., 2002). The symbols for sequences are shown in Table 1. The numbers at nodes in the tree indicate BPs (%) obtained from 1000 replicates (only those for major clusters are shown). SC subgroups (SC-a to -f and SC-x) are indicated. Isolates whose sequences were determined in the current study are shown in white on a black background, while those whose sequences were determined previously (but left unclassified into subgroups) are shown in white on a grey background.

Table 2. Worldwide distribution of SC subgroups classified by phylogenetic analysis of complete viral DNA sequences

Geographic origin	Total no. of isolates analyzed	No. of isolates classified as[1]:							
		SC-x	SC-a	SC-b	SC-c	SC-d	SC-e	SC-f	Other[2]
China	14	0	1	0	0	0	0	13	0
Vietnam	3	0	0	0	0	0	0	3	0
Thailand	3	0	2	0	1	0	0	0	0
Myanmar	22	0	0	1	3	6	4	7	1
Malaysia	3	0	0	0	0	0	0	3	0
Indonesia	2	0	0	0	0	0	0	2	0
Philippines	12	6	0	0	0	0	0	6	0
Mongolia	1	0	0	1	0	0	0	0	0
Mauritius	2	0	0	0	0	0	0	2	0
Zambia	1	0	0	0	0	0	0	1	0
South Africa	1	0	0	0	0	0	0	1	0
Hawaii, USA	1	1	0	0	0	0	0	0	0
Total	65	7	3	2	4	6	4	38	1
	(24)	(1)	(1)					(21)	(1)

[1] Numbers within parentheses indicate isolates classified into subgroups in the present study.
[2] One isolate (RH-2) was classified as 'other' since this isolate did not cluster with any other isolates in the analysis (Figure 2).

Table 3. Worldwide distribution of SC-f and non-SC-f isolates based on an SNP within the VT-intergenic region

Geographic region	Total no. of SC isolates	No. of SC isolates grouped as[1]		Ref.[2]
		SC-f	Non-SC-f	
NE China (Harbin, Shenyang, Manzhouli, Chifeng)[3]	7	5	2	A, B
NW China (Xi'an, Lanzhou, Urumqi)	8	8	0	C
SE China (Wuhan, Guangzhou, Taipei)	19	17	2	A
SW China (Chengdu, Kunming, Lhasa)	12	10	2	A, B, D
Thailand (Chiang Mai)	11	3	8	A
Myanmar (Myitkyina)	15	3	12	E
Myanmar (Tiddim)	27	0	27	E
Myanmar (Chaungtha Beach)	10	4	6	E
Myanmar (Yangon)	9	2	7	E
Myanmar (Peinnebeen)	21	18	3	E
Vietnam (Hanoi)	18	18	0	D
Vietnam (Danang)	26	26	0	D
Malaysia (Masai)	13	13	0	A
Indonesia (Jakarta)	17	16	1	A
Philippines (Pamalican Is.)	4	4	0	A
Philippines (Luzon)	13	8	5	F
Philippines (Cebu)	17	11	6	F
Philippines (Mamanwa)	6	6	0	G
Mauritius (Port Louis)	3	3	0	A
Zambia (Lusaka)	1	1	0	A
South Africa (Kwazulu-Natal)	1	1	0	H
USA (Guam)	8	8	0	I
USA (Hawaii)	1	0	1	J
S Japan	8	8	0	K
Total	275	193	82	

[1] Most isolates were classified based on an SNP that subclassifies SC isolates into SC-f and non-SC-f (see text), but those in Guam, USA were classified as SC-f based on the presence of the unique pentanucleotide deletion in the regulatory region of the viral genome.
[2] A, Sugimoto et al. (1997); B, Cui et al. (2004); C, Guo et al. (2001); D, Saruwatari et al. (2002a); E, Saruwatari et al. (2002b); F, Miranda et al. (2003); G, Miranda et al. (2004); H, Venter et al. (2004); I, Ryschkewitsch et al. (2000); J, Yanagihara et al. (2002); K, Kitamura et al. (1998).
[3] Including Mongolia (Ulaanbaatar), where a single SC isolate was reported (Sugimoto et al., 1997).

Classification of SC isolates worldwide into SC-f and non-SC-f subgroups, based on an SNP

Partial DNA sequences [i.e. 610-bp VT-intergenic sequences (Ault and Stoner, 1992)] have been reported for many SC isolates, but the complete genomic sequences of these isolates remain undetermined. We examined these sequences to determine if they included SNPs that might be used to classify the SC isolates into SC-f and non-SC-f subgroups. By aligning the 65 complete SC DNA sequences (Table 1), we identified one such SNP at nucleotide 2419 (the nucleotide numbering is that of isolate TL-5). All isolates classified into the SC-f subgroup based on complete sequences (Figure 2) carried A at this polymorphic site, while all isolates classified as SC-a to -e and SC-x (desig-

nated non-SC-f) had G at this position. Based on this SNP, we subclassified a large number of SC isolates worldwide into SC-f or non-SC-f subgroups (Table 3).

The findings shown in Table 3 can be summarized as follows: (1) SC-f isolates predominated in all regions of China, with only the occasional occurrence of non-SC-f; (2) non-SC-f isolates predominated in one region of Thailand and most regions of Myanmar, with the exception of Peinnebeen, where isolates classified as SC-f were mainly detected; (3) SC-f isolates predominated in two regions of Vietnam and in single regions in Malaysia and Indonesia; (4) SC-f isolates predominated in three islands in the Philippines, although non-SC-f isolates occurred at lower but significant rates ($P < 0.01$ vs. Hanoi and Danang; Fisher's exact test) in two islands (Luzon and Cebu) of the Philippines, these were previously identified as a unique subgroup (SC-x) of the SC genotype (Miranda et al., 2003; Takasaka et al., 2004); (5) only SC-f isolates occurred in regions (e.g. southern Africa and southern Japan) remote from the areas where SC is most common (i.e. Southeast Asia), although these were detected at only a low frequency (Sugimoto et al., 1997; Kitamura et al., 1998); (6) most SC isolates in Guam probably belonged to the SC-f subgroup, as these had the unique pentanucleotide deletion in the regulatory region (see above). In addition, a single isolate in Hawaii was grouped in the non-SC-f category based on the SNP analysis, consistent with the phylogenetic analysis of the complete viral DNA sequences described above.

We statistically analyzed the data shown in Table 3 using the chi-square test with Yates' correction and Fisher's exact test, and found that the distribution of SC-f and non-SC-f in Thailand and Myanmar was significantly different from that in the other geographic regions excluding Luzon and Cebu, the Philippines ($P < 0.01$). Thus, in general, the results of the SNP analysis of the 275 SC isolates were consistent with those from the phylogenetic analysis of 65 complete SC isolates.

Discussion

In this study, we classified 65 SC isolates worldwide into seven subgroups (SC-a to -f, and SC-x) using a phylogenetic analysis based on complete DNA sequences, supplemented by the presence or absence of a unique pentanucleotide deletion in the regulatory region. We then performed an SNP analysis of 275 reported partial DNA sequences of SC isolates. From the results of these analyses, we conclude that SC-f isolates are widespread in the world, but that most non-SC-f isolates are restricted to an area of mainland Southeast Asia including Myanmar and Thailand (and probably part of South China), with some exceptions in the SC-x subgroup, which were found mainly in the Philippines.

Cui et al. (2004) classified many JCPyV isolates detected in China as Type 7A, and proposed that these isolates represent one of the typical Chinese JCPyV genotypes. As described above, most of the Type 7A isolates detected by Cui et al. belong to the SC-f subgroup, with the exception of 732A. Furthermore, we showed that isolates of the SC-f subgroup extend over a wide domain, including China and all Southeast Asian countries, with the eastern edge of this area in southern Japan and the western edge in southern Africa. Therefore, it is now misleading to characterize Type 7A as a genotype of JCPyV unique to the Chinese population.

SC-f is found over such a wide geographic region that it is hard to identify a particular region as its area of origin. On the other hand, most of the non-SC-f isolates of the SC-a to -e subgroups were essentially located in Myanmar and Thailand, while the SC-x isolates occurred mainly in the Philippines. Assuming that JCPyV evolved with division of human populations (Yogo et al., 2004), the present pattern of distribution of various SC subgroups may be explained as follows. In an area of Southeast Asia including Myanmar and Thailand (the circled area in Figure 1), an ancestral human population carrying proto-SC may have diverged into various populations, each carrying a distinct variant of SC (e.g. those carrying SC-a to -f and SC-x). Among these human populations, only a few (those carrying the SC-f and SC-x subgroups) migrated out of the area.

Human dispersals in the Pacific are thought to have been executed mainly by populations carrying three Pacific genotypes of JCPyV, namely 2E, 8A, and 8B (Jobes et al., 2001; Yanagihara et al., 2002; Takasaka et al., 2004). However, it appears that Southeast Asians carrying SC genotypes of JCPyV also contributed, at least in part, to the dispersals in the Pacific. For example, the SC-f isolates may reflect human migrations to the Pacific islands (e.g. Guam) near mainland Asia (Ryschkewitsch et al., 2000; Jobes et al., 2001; Takasaka et al., 2004). The detection of SC-x in Hawaii (Yanagihara et al., 2002), albeit at a low rate, suggests a novel human migration carrying the SC-x subgroup from island Southeast Asia, as this genotype is relatively common among modern Filipinos (Miranda et al., 2003; Takasaka et al., 2004). In addition, Takasaka et al. (2006) recently detected a new SC subgroup (named SC-g) in Kiribati islanders at a low but significant frequency. The detection of SC-g in Kiribati might reflect another human migration from Southeast Asia. However, the available information regarding the distribution of SC genotypes in the Pacific remains fragmentary, and genetic analysis of a large number of JCPyV isolates from various Pacific islands is needed to provide further information on the dispersal of Southeastern Asians into the Pacific.

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AIDS 関連カリニ肺炎の診断から治療までのコツ

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日本では HIV 感染者/AIDS 患者が着実に増えており，しかも AIDS 患者の多くは AIDS を発症するまで HIV 感染の事実を自らも把握していない．未治療の HIV 感染者が AIDS を発病する場合，カリニ肺炎を AIDS 指標疾患として発症することが比較的多い．カリニ肺炎を発症した AIDS 患者が HIV/AIDS 専門病院を初めから受診することは少なく，一般内科医や呼吸器科医を受診していることが多い．AIDS 関連カリニ肺炎を診断するためには，まず患者の HIV 感染を疑うことから始まる．

AIDS 関連カリニ肺炎は症状の進行が緩徐

自覚症状は発熱，咳嗽（乾性咳嗽のことが多い），労作時呼吸困難が多く，AIDS 関連カリニ肺炎に特異的なものはない．ただし他の免疫不全患者に発症するカリニ肺炎に比較して，多くの症例で症状進行が緩徐であることは特徴の一つである．

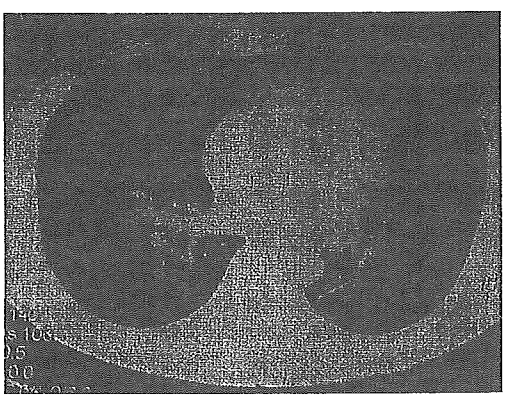
カリニ肺炎を発症する AIDS 患者ではしばしば口腔カンジダ症や脂漏性皮膚炎を認め，これが HIV 感染を疑う契機となるので診察時注意しておくべきである．口腔カンジダ症の病変には偽膜性，過形成性，紅斑性がある．偽膜性，過形成性は白色の病変で目立つが，紅斑性は口腔粘膜の赤っぽい斑点であり，時に口腔カンジダ症と認識しにくいことがあるので注意が必要である．脂漏性皮膚炎は眉間，頬部，顎髭部などの顔面にみられ，通常は左右対称性の桃色ないし赤色の皮膚炎で，明瞭な鱗屑を伴っている．

また性的接触による HIV 感染者では他の性感染症（STD）をしばしば合併する．梅毒，クラミジア感染症，性器ヘルペス，ウイルス性肝炎などの診断が HIV 感染症の診断に先行することもあるので，詳細な病歴聴取や診察が重要である．

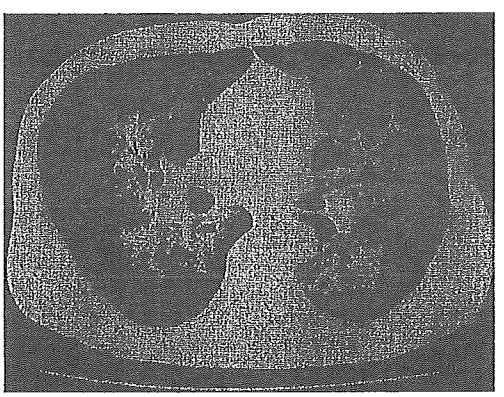
胸部所見としてスリガラス陰影を認めることが多い

AIDS 関連カリニ肺炎の胸部 X 線写真はびまん性スリガラス陰影であることが多いが，時に陰影濃度の濃い浸潤影がみられることもある．気胸は AIDS 関連カリニ肺炎ではしばしば合併する．

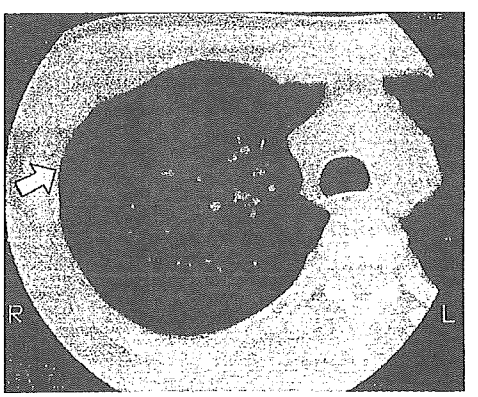
胸部 CT 所見は血管影を透過できるスリガラス状の肺野濃度上昇を認めることが多く（❶），その分布は区域性のない地図状分布が特徴的である．胸膜面に平行するような濃厚な帯状の濃度上昇や血管陰影を透過できない肺野濃度上昇域（❷）を伴ったりもする．気管支拡張や嚢胞形成（❸）も比較的よ



❶カリニ肺炎でよくみられる胸部 CT 所見
スリガラス状の肺野濃度上昇があり，カリニ肺炎で最も多いパターンである．



❷濃厚な肺野濃度上昇を認めた胸部 CT 所見



❸嚢胞形成を認めた胸部 CT 所見
しばしば嚢胞形成（矢印）を認め，本例は気胸を合併した．

く認められる所見である．

AIDS関連カリニ肺炎の検査所見の把握

CD4陽性リンパ球数が200/μL未満となると，AIDS関連カリニ肺炎を発症する危険性があるとされている．しかし実際にAIDS関連カリニ肺炎を発症している症例の大半はCD4陽性リンパ球数が100/μL以下である．CRPは陽性であることが多いが，その値は多くの症例で10mg/dL以下である．LDHは上昇していることが多く，動脈血酸素分圧と負の相関を認め，カリニ肺炎の重症度の指標ともなりうる．

*Pneumocystis carinii*は遺伝子学的解析で真菌に類似性が高く，シスト細胞壁の主要構成成分にβ-D-グルカンが含まれている．そのためカリニ肺炎時に血清β-D-グルカン値が上昇する．またKL-6は肺胞II型上皮細胞から産生，分泌され，肺胞II型上皮細胞の過形成を伴う間質性肺疾患の病勢指標の一つである．カリニ肺炎の病理学的所見では肺胞II型上皮細胞の増生を認めるとされ，カリニ肺炎発症時に血中KL-6値が上昇する．したがってβ-D-グルカン値とKL-6値とがともに上昇している場合にはカリニ肺炎を強く疑う所見であり，補助診断法として有用である．

第一選択薬SMX/TMPは投与量の再評価が必要

カリニ肺炎治療の第一選択薬はスルファメトキサゾール/トリメトプリム（SMX/TMP）であり，内服薬と点滴薬とが市販されている．AIDS関連カリニ肺炎での本薬剤の投与量はSMX 75～100mg/kg/日・TMP 15～20mg/kg/日が標準的である．しかし，われわれの施設では軽・中等症のAIDS関連カリニ肺炎症例に対して，この標準投与量の半量でも十分な治療効果を得ており，SMX/TMPの適切な投与量を再評価する必要があると考える．HIV感染者ではSMX/TMPの副作用発現頻度が50～60%であり，発熱，発疹，白血球減少，肝機能障害などが比較的早期（投与後7～10日目）に認められることが多い．SMX/TMPを減量しても副作用の発現率には差はないが，重篤な副作用が少なくなる印象がある．

SMX/TMPを用いることができない場合にはペンタミジン3～4mg/kg/日を1日1回点滴静注する．ペンタミジン吸入はカリニ肺炎予防には用いるが，治療目的の場合には効果が弱いので行うべきではない．軽・中等症の場合にはダプソン100mg/日の内服治療も可能である．治療期間は一般的に21日間とされているが，これは最短治療期間と考え，症状，検査所見（特に動脈血酸素分圧あるいは酸素飽和度），胸部画像所見などを総合的に判断して，治療を終了する．

大気圧下の動脈血酸素分圧が70 Torr未満の場合には副腎皮質ステロイド薬の併用投与が有効である．われわれの施設ではプレドニゾロン60～80mg/日で投与を開始し，4～5日ごとに減量し，2週間ほどで中止している．重症例の場合にはステロイドパルス療法を行うこともある．しかしAIDS関連カリニ肺炎ではしばしば気胸を合併し，副腎皮質ステロイド薬がその誘引となることも指摘されている．またカリニ肺炎を発症時にすでに他の日和見感染症を合併していたり，治療中に合併したりすることがあるので，漫然と副腎皮質ステロイド薬を投与することは厳に慎むべきである．

HAARTでAIDS関連カリニ肺炎予防の中止を考慮

HIV感染者ではカリニ肺炎未発症でもCD4陽性リンパ球数が200/μL未満の場合（一次予防）やカリニ肺炎治療後（二次予防）に予防投薬が必要である．予防薬は治療薬と同様で，SMX/TMP，ペンタミジン，ダプソンが用いられ，ペンタミジン吸入がオプションに加わる．

SMX/TMPはSMX 400mg・TMP 80mg（1錠あるいは1g）/日で投与するが，治療と同様に副作用を認めることが多い．発熱，発疹などのアレルギー機序が関与する副作用は脱感作療法で回避できるようになることがあるので試みる価値がある．またペンタミジン吸入は300mgを1回/4週で投与する方法で，しばしばカリニ肺炎の発症を認めることから，われわれの施設では300mgを1回/2週で吸入する方法を選択している．さらにペンタミジン吸入を3年以上の長期間行っている症例では呼吸機能検査上細気道障害の変化がみられることから，長期予防を避ける必要があると考えている．

強力な抗HIV治療（HAART）が行われ，免疫能が改善されるようになり，カリニ肺炎予防の中止が考慮されている．現在，CD4陽性リンパ球数が200/μL以上を3か月以上継続した場合，一次・二次予防とも中止が可能であるとされている．われわれの施設でも免疫能の改善に伴ってカリニ肺炎予防を中止した症例で，これまでにカリニ肺炎を発症したことはまったくない．

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ORIGINAL ARTICLE

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Aerosolized pentamidine prophylaxis against AIDS-related *Pneumocystis carinii* pneumonia and its short- and long-term effects on pulmonary function in the Japanese

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Abstract We evaluated the incidence of prophylaxis failure with aerosolized pentamidine (AP) for *Pneumocystis carinii* pneumonia (PCP) in Japanese patients with human immunodeficiency virus (HIV) infection, and we examined the short- and long-term effects of AP on pulmonary function. The patients inhaled 300 mg of pentamidine by ultrasonic nebulizer, after the inhalation of procaterol (80 μg), every 4 weeks. PCP developed in 2 of 16 patients receiving primary prophylaxis with AP, and in 4 of 13 patients with secondary prophylaxis. The $CD4^+$ T-lymphocyte count was very low in the patients with prophylaxis failure. The chest radiographic presentations were atypical in 4 of the 6 patients with prophylaxis failure. There were no significant changes in the vital capacity (VC), VC/predictive VC (%VC), forced expiratory volume in 1 s ($FEV_{1.0}$), $FEV_{1.0}$/forced vital capacity ($FEV_{1.0}$%), and maximum expiratory flow rate at 25% of vital capacity (MEF_{25})/height comparing values before and after initial AP treatment. However, a reduction of oxygen saturation (SpO_2) of over 3% was noted in 4 patients during the initial AP administration. In 9 patients receiving AP prophylaxis for more than 36 months, we compared the pulmonary function parameters between the baseline and final observations (mean, 52.7 months). There were no changes in VC, %VC, $FEV_{1.0}$, $FEV_{1.0}$%, and SpO_2, but there was a statistically significant decline in MEF_{25}/height after long-term AP treatment. We concluded that the incidence of prophylaxis failure with AP for PCP in Japanese patients was similar to that in Western patients, and that long-term AP treatment affected MEF_{25}/height in spite of the safe pulmonary effects in short-term AP inhalation.

Key words Aerosolized pentamidine · Prophylaxis failure · *Pneumocystis carinii* pneumonia · Pulmonary function · Human immunodeficiency virus infection

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Introduction

Pneumocystis carinii pneumonia (PCP) is still one of the most common opportunistic infections in human immunodeficiency virus (HIV)-positive patients with advanced immune impairment. Therefore, HIV-infected patients who have a $CD4^+$ T-lymphocyte count of less than 200/μl, or a history of PCP, should receive chemoprophylaxis against PCP.[1] Most clinicians consider trimethoprim-sulfamethoxazole (TMP-SMX) as the recommended agent for PCP prophylaxis. However, the prophylactic regimen of TMP-SMX is frequently discontinued due to various adverse events.[2] Aerosolized pentamidine (AP) is considered a second-line prophylactic drug for HIV-positive patients who cannot tolerate TMP-SMX, because AP has few systemic adverse effects.

There is still no report about the prophylactic efficacy or pulmonary effects of AP in Japan. The objectives of this study were to determine the incidence of prophylaxis failure, and to evaluate the short- and long-term effects on pulmonary function in Japanese HIV-infected patients receiving AP for PCP prophylaxis.

Patients and methods

Patients

Twenty-nine HIV-positive Japanese patients, who received AP for PCP prophylaxis because of intolerance to TMP-

SMX, were enrolled between 1990 and 2001. They had no underlying respiratory disease nor any abnormal findings on chest roentgenogram at the start of AP therapy. We prospectively observed the incidence of prophylactic failure for PCP in these patients. Spirometry (vital capacity [VC], VC/predictive VC [%VC], forced expiratory volume in 1 s [$FEV_{1.0}$], $FEV_{1.0}$/forced vital capacity [FVC] [$FEV_{1.0}$%], and maximum expiratory flow rate at 25% of vital capacity [MEF_{25}]/height) was performed before and after the initial AP treatment, and oxygen saturation (SpO_2) was measured during the first AP administration. Their mean age at starting AP prophylaxis was 38.5 years (range, 18–71 years), and 27 of the 29 patients were males. The risk factors for HIV infection were intravenous administration of non-heated blood products in 18 patients, heterosexual transmission in 10, and homosexual transmission in 1. The mean $CD4^+$ T-lymphocyte count was 58.1/μl (range, 2–178/μl). Sixteen patients were classified as receiving AP for primary prophylaxis because they had had no prior episodes of PCP. Thirteen patients were categorized as receiving secondary prophylaxis because they had had a prior episode of clinically diagnosed or laboratory-confirmed PCP.

Nine of the 29 patients received AP for over 36 months (average, 52.7 months; range, 36–58 months). Their mean age at the final observation was 41.7 years (range, 28–55 years). All these patients were males. We compared their pulmonary function test results (VC, %VC, $FEV_{1.0}$, $FEV_{1.0}$%, MEF_{25}/height, and SpO_2) between the baseline and final observations at more than 36 months after the start of AP treatment.

All patients were examined after their informed consent was obtained.

AP protocol

AP treatments were administered with an ultrasonic nebulizer (Nesco Ultrasonic Nebulizer UN-70; Aika, Tokyo, Japan; aerosol particle size, 3–5 μm). The patients inhaled 80 μg of procaterol hydrochloride for approximately 5 min prior to the inhalation of AP. Then, they inhaled 300 mg of pentamidine isetionate dissolved in 10 ml of sterile water over a period of 15 to 30 min. They inhaled the aerosol via a mouthpiece, utilizing spontaneous tidal volume breathing while sitting upright. AP treatments were administered every 4 weeks.

Statistical analysis

The two-tailed paired Student's *t*-test was used for the statistical comparison of continuous variables. A *P* value of less than 0.05 was considered statistically significant.

Results

Prophylaxis failure of AP

The total number of prophylaxis failures against PCP in the 29 patients was 6 during a mean follow-up time of 24.5 months (range, 3–82 months). The frequency of breakthrough episodes was 2 in the 16 patients with primary prophylaxis (mean observation time, 27.8 months; range, 6–82 months) and 4 in the 13 patients with secondary prophylaxis (mean observation time, 20.5 months; range, 3–52 months) (Table 1).

PCP developed within 6 months after the start of AP prophylaxis in four of the six patients. The $CD4^+$ T-lymphocyte count was very low in the patients with prophylaxis failure against PCP. The radiographic findings showed predominantly upper lung field infiltrates in two patients, diffuse interstitial infiltration in two, bilateral pneumothorax with cystic lesions in one, and predominantly left lung field infiltrates with pleural effusion in one (Table 1).

Pulmonary function at the initial AP treatment

The VC was 3844 ± 655 ml (mean ± SD) at the baseline and 3784 ± 697 ml after AP. The %VC was 101.8 ± 13.8% before AP and 101.1 ± 14.3% after AP. The absolute $FEV_{1.0}$ values before and after AP were 3065 ± 691 ml and 3065 ± 697 ml, respectively. The $FEV_{1.0}$% was 82.6 ± 6.3% at baseline and 82.5 ± 5.3% after AP. The MEF_{25}/height was 0.87 ± 0.22 l/s per m before AP and 0.87 ± 0.22 l/s per m after AP. There were no significant changes in VC, %VC, $FEV_{1.0}$, $FEV_{1.0}$%, and MEF_{25}/height comparing values before and after AP treatment (Fig. 1).

A reduction in SpO_2 of more than 3% was noted in four patients (13.8%) during the initial AP treatment. They could be divided into two groups according to the change of $FEV_{1.0}$ after AP administration. SpO_2 declined with reduc-

Table 1. Background and chest radiographic presentations in HIV-infected patients with prophylactic failure of aerosolized pentamidine

Case no.	Age (years)	Sex	Prophylaxis	Period of AP (months)	$CD4^+$ count (/μl)	Radiographic findings
1	30	Male	Primary	6	5	Predominantly upper lung field infiltrates
2	32	Female	Primary	6	6	Diffuse interstitial infiltration
3	22	Male	Secondary	17	11	Bilateral pneumothorax with cystic lesions
4	25	Male	Secondary	3	8	Diffuse interstitial infiltration
5	40	Male	Secondary	17	2	Predominantly left lung field infiltrates with pleural effusion
6	47	Male	Secondary	5	3	Predominantly upper lung field infiltrates

AP, Aerosolized pentamidine

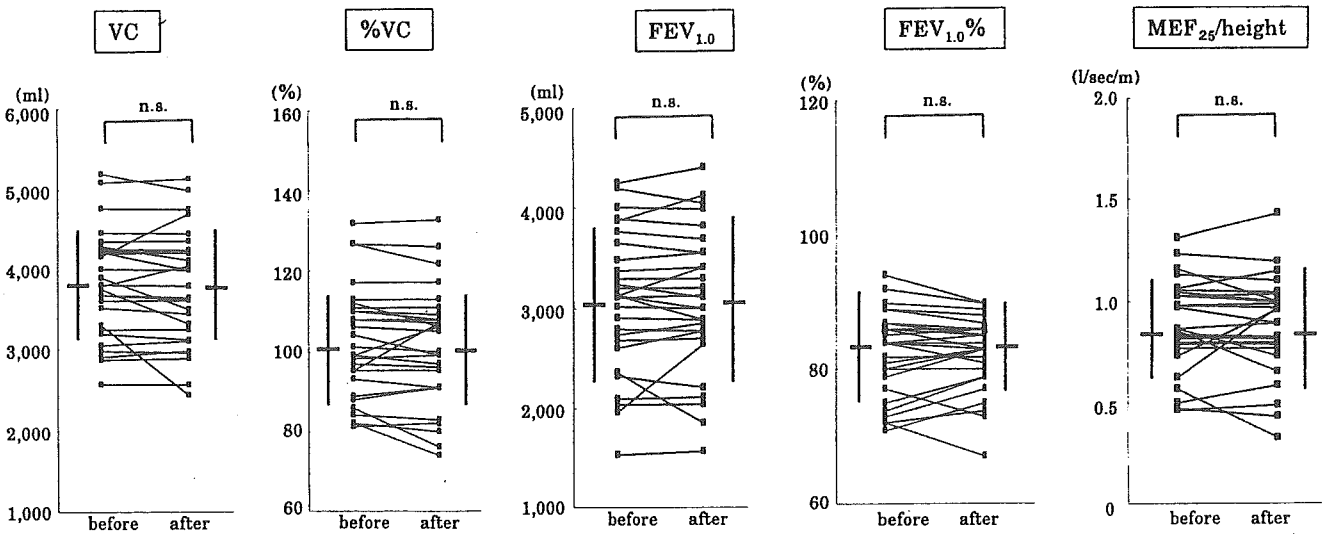

Fig. 1. Changes in pulmonary function comparing values before and after the initial aerosolized pentamidine treatment. *VC*, Vital capacity; *%VC*, VC/predictive VC; *$FEV_{1.0}$*, forced expiratory volume in 1 s; *$FEV_{1.0}$ %*, $FEV_{1.0}$/forced vital capacity; *MEF_{25}*, maximum expiratory flow rate at 25% of vital capacity; *n.s.*, Not significant

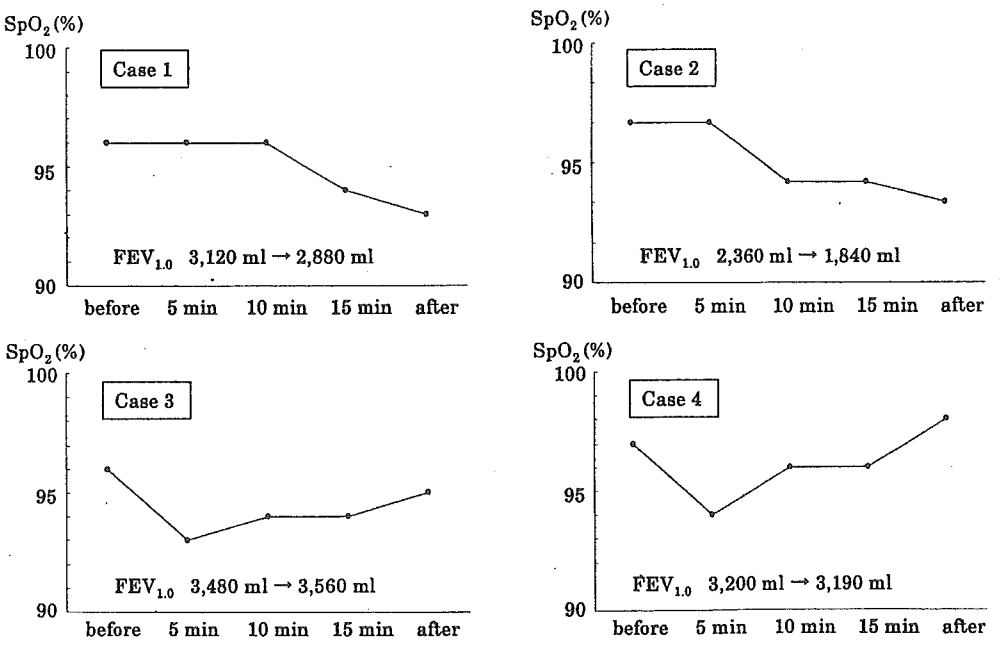

Fig. 2. Correlation between SpO_2 decline (more than 3%) in four patients and changes of $FEV_{1.0}$. *SpO_2*, Oxygen saturation; *$FEV_{1.0}$*, forced expiratory volume in 1 s

tion of $FEV_{1.0}$ in one group of two patients and without reduction of $FEV_{1.0}$ in the other group of two patients (Fig. 2).

Pulmonary function after long-term AP treatment

There were no changes in VC, %VC, $FEV_{1.0}$, $FEV_{1.0}$%, and SpO_2 between the baseline and final observations. However, there was a statistically significant decline in MEF_{25}/height after long-term AP treatment (mean treatment period, 52.7 months; Fig. 3).

Discussion

Pentamidine is one of a family of guanidine analogues that were discovered to have antiprotozoal activity. The rate of adverse reactions is high in patients with intramuscular or intravenous administration of pentamidine. AP inhalation has a low incidence of systemic adverse reactions,[3] because pentamidine can be nebulized and delivered directly to the lungs with minimal systemic absorption. Although AP has not been recommended for the treatment of AIDS-related PCP, there is considerable evidence about its efficacy in

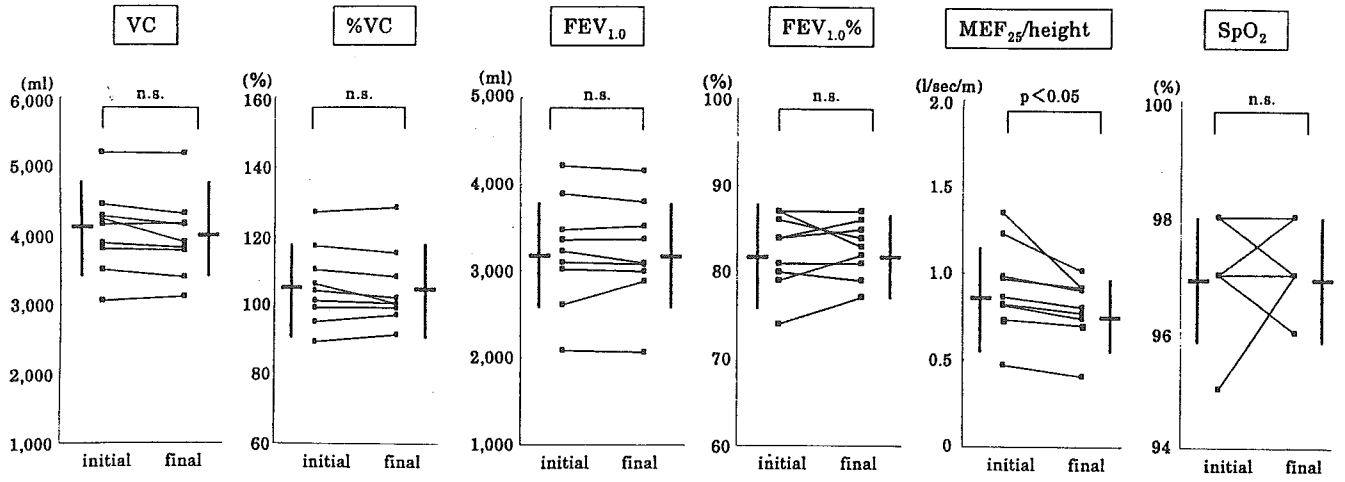

Fig. 3. Changes in pulmonary function after longterm aerosolized pentamidine treatment. *VC*, Vital capacity; *%VC*, VC/predictive VC; *$FEV_{1.0}$*, forced expiratory volume in 1 s; *$FEV_{1.0}$%*, $FEV_{1.0}$/forced vital capacity; *MEF_{25}*, *height*, maximum expiratory flow rate at 25% of vital capacity; *SpO_2*, oxygen saturation; *n.s.*, not significant

both primary and secondary prophylaxes against PCP.[2,4] We found that the failure rate of primary prophylaxis was 12.5% in the Japanese patients receiving AP, and that the failure rate of secondary prophylaxis was 30.8%. These rates are similar to those in previously published reports in Europe and the United States. The incidence of breakthrough PCP in patients using AP for primary prophylaxis was between 8.6% and 23.0% in previous studies.[5,6] The failure rates of secondary prophylaxis were between 19.8% and 36.1% in various reports about long-term follow-up.[2,7,8] On the other hand, TMP-SMX was more effective than AP therapy in both primary and secondary prophylaxis against AIDS-related PCP in several trials.[2,4] Therefore, we also consider that TMP-SMX should be used as a first-line agent for PCP prophylaxis in HIV-positive patients.

Wei et al.[7] showed that a low $CD4^+$ T-lymphocyte count and previous infection with PCP were important risk factors for prophylaxis failure. We also found that the $CD4^+$ T-lymphocyte count was low, less than 11/μl, in the patients with prophylaxis failure against PCP, and that the prevention failure rate in the patients receiving AP for secondary prophylaxis was higher than that for primary prophylaxis.

Several studies reported that the administration of 300 mg AP twice monthly was more effective than 300 mg AP once monthly as prophylaxis against PCP.[9,10] In addition, Yamamoto et al.[11] measured the concentration of pentamidine in the bronchial epithelial lining fluid after the administration of AP (300 mg) to sheep, and they found a rapid clearance of the inhaled pentamidine from the bronchial wall within the first 2 weeks. Therefore, we consider that we should select 300 mg AP twice monthly for prophylaxis against AIDS-related PCP as a standard regimen now.

Chest roentgenograms reveal bilateral interstitial infiltrates, which spread from the perihilar region to the lung periphery in the majority of patients with PCP. However, atypical roentgenographic presentations are often noticed in HIV-infected patients receiving AP prophylaxis. Kennedy and Goetz.[12] stated that the incidence of PCP-associated upper lobe disease, cysts, and spontaneous pneumothorax was increased in patients who received AP prophylaxis. We also found that the chest radiographic findings were atypical in four of six patients with PCP, despite AP prophylaxis. Therefore, it is necessary for us to thoroughly understand that the roentgenographic manifestations are often unusual in patients receiving AP prophylaxis against AIDS-related PCP.

It has been recommended that patients receive a bronchodilator before AP treatment,[13] because AP commonly induces bronchospasm and coughing attacks. Therefore, we administered a procaterol hydrochloride (β_2-agonist) inhalation as premedication before AP in the present study. This study showed that there were no significant changes in pulmonary function parameters (VC, $FEV_{1.0}$, and MEF_{25}/height) comparing values between before and after the initial AP treatment. However, a reduction of SpO_2 of more than 3% was noted in four patients during inhalation of AP. The reduction of SpO_2 was related to bronchospasm in two patients. On the other hand, the reason that SpO_2 temporarily declined without reduction of $FEV_{1.0}$ in the other patients was unknown. Therefore, we consider that it is necessary to observe SpO_2 during the initial AP treatment, although there are no acute effects of AP on pulmonary function.

In this study, AP treatment of more than 36 months for PCP prophylaxis in HIV-infected patients was associated with a decline of MEF_{25}/height, which indicated impairment of the small airways. There were no changes in VC, %VC, $FEV_{1.0}$, $FEV_{1.0}$%, and SpO_2 over the long-term period. Wei et al.[14] evaluated pulmonary function in 179 patients receiving AP for at least 24 months, and they reported that there was a statistically significant decline in the total lung capacity, FVC, residual volume, $FEV_{1.0}$, $FEV_{1.0}$%, and MEF_{50} after a mean duration of 23.8 months. Accordingly, long-term AP therapy may affect pulmonary function. However, the results in our study were different from those in the report by Wei et al.,[14] because the pulmonary function parameters, except for MEF_{25}/height, did not change in our study. The main difference between our study and their

report was the sample size. It might be difficult to recognize changes in lung function parameters without a large sample size, because the pulmonary function values after 24 months were all within the normal ranges in their report. In fact, there were reports that concluded that long-term AP therapy did not affect pulmonary function in small cohorts of patients.[15] Camus et al.[16] suggest that the bronchial toxicity and airway irritation may be due to the thiol derivatives contained in the pentamidine salts or the acidity of the pentamidine solution. Hiles et al.[17] histopathologically demonstrated the respiratory toxicity of AP inhalation in rats and dogs. The long-term pulmonary effects of AP may be related to repeated bronchial toxicity or airway irritation over the long period. Further studies should be undertaken to elucidate the mechanism of pentamidine's long-term pulmonary effects. In addition, we should discontinue AP prophylaxis for PCP as early as possible if there is an increase in $CD4^+$ T-lymphocyte count responding to highly-active antiretroviral therapy in HIV-infected patients with advanced disease.

In conclusion, this study showed that the incidence of prophylaxis failure with AP against PCP in Japanese HIV-infected patients was similar to that in Western patients, and that long-term AP treatment affected MEF_{25}/height in spite of the safe pulmonary effects in short-term AP inhalation.

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CCR5のイントロン内の変異と連鎖しているため，これらの変異によってCCR5の発現量が微妙に低下するためにAIDS病態の進行や感染抵抗性に影響する可能性が一つ考えられる[4]。一方，野生型のCCR2はCXCR4とはヘテロ二量体を形成できないが，変異を持つCCR2はCXCR4と二量体を形成できることが報告された。このCXCR4とのヘテロ二量体形成能の違いが何らかの機構でAIDS病態進行を遅延させている可能性も考えられている[5]。

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V. 臨床

10. CMV網膜炎による失明で長期入院していた症例における退院への支援

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はじめに

治療の進歩によりHIV感染症の予後が改善した一方で，HIV感染者はさまざまな問題とも直面している。今回われわれは，CMV網膜炎のため両眼を失明し，家庭の事情などから長期入院を続けていたHIV感染者に対して在宅療養に向けて支援し実現できたので，その経験を報告する。

症例の経過

症例：52歳，男性。

病歴：異性間性的接触のためHIVに感染し，1996年4月に当科を紹介された。受診直後にカリニ肺炎を発症したが，治療により治癒し，社会復帰していた。同年10月に右眼CMV網膜炎を認め，11月5日に入院した。ガンシクロビル・ホスカルネットで治療したが，副作用による治療中断等のため1998年1月に両眼を失明した。

経過：失明で行動範囲が制約されたので1998年4月からボランティア(ならHIVネットワーク)を依頼し，院外への買い物・運動などの介助をしてもらった。医療費・収入などの点から身体障害の取得を勧めていたが，キーパーソンである義兄が免疫機能不全での申請をプライバシーへの不安から拒否したため，12月に視力障害で身体障害1級を取得した。

1999年2月に義兄を交えて今後のことを話し合うが，母親の介護などのため自宅への退院後の受け入れは無理であると回答された。現状の活動能力では退院は困難であり，7月から視力障害者支援団体であるライトハウスによる中途失明者生活訓練を開始した。また，患者本人の思いを知るためにも11月からカウンセリングを再開した。

2000年1月に地域福祉課・義兄と面談したが，義兄は自宅での受け入れは無理なので施設入所を希望した。3月に養護施設への入所が可能となったが，施設へ入所すると制度的にライトハウスの訓練を継続することが無理なため，訓練を継続したい患者本人の希望を尊重し入院を継続することとなった。

表　症例の経過

年	月	状況	対応
1996	4	HIV 感染症で受診，カリニ肺炎発症	入院加療
	10	CMV 網膜炎発症	入院加療，副作用で治療中断
1998	1	両眼失明	
	4	行動範囲の制約	ボランティアの依頼
	12	医療費・収入の問題	視力障害で身体障害1級を取得
1999	2	義兄と話し合い→自宅退院を拒否	
	7	活動能力が不十分	中途失明者生活訓練を開始
	11		カウンセリングを再開
2000	1	義兄と話し合い→施設入所を希望	
	3	養護施設入所が可能	患者が訓練継続のため入院を希望
2001	1	義兄と話し合い→独居での退院を希望	
	7	義兄入院→自宅退院を受け入れ	
	11		医療スタッフで退院支援計画
2002	1		医療スタッフで支援の達成状況評価
	2		関係者で退院後の問題点を検討
		1,930 日ぶりに自宅へ退院	
	3	定期通院・訓練の継続	

2001年1月に再度地域福祉課・義兄と面談し，独居での退院を目指すこととなったが，最適な住居が見つからず，めどが立たなかった。7月に義兄自身が入院し，入院の味気なさを体験したことから自宅への受け入れを了承し，自宅の改造などを始めた。そこで11月に医療スタッフで検討会を開催し，退院へ向けての支援計画を立て，実施した。医師は病気・治療についての再教育，薬剤師・看護師は服薬の自己管理，MSW は福祉的支援，カウンセラーは心理的支援などを課題として取り組んだ。退院日が2002年2月中旬と決まったので，1月には医療スタッフで支援の達成状況を検討した。また，2月4日には医療スタッフ・ライトハウス・地域福祉課・義兄で退院後の問題点などを話し合い，プライバシーの点から地域スタッフのサービスを当面は受けずに対応することとなった。そこで，他地域の訪問看護ステーションからサポートを受けることにして，そのスタッフを紹介した。2月16日に自宅への退院がついに実現し，1,930日間の入院生活を終えた。その後も義兄の助けを借りて定期的に通院を続けると共に，自宅で視力障害者訓練を継続している(表)。

考　察

HIV 感染者はプライバシーなどの点から容易に地域の福祉サービスを受け難く，その点を配慮した支援が必要であった。また，HIV 感染者の支援には医学的な対応だけでは限界があるため，病院内外の多職種(ボランティアも含む)との連携が不可欠であり，そのためには院内や地域での支援ネットワーク作りが急務な課題であると感じた。

10. 当科におけるリポジストロフィー症例の現状

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はじめに

強力な抗HIV治療(HAART)によりHIV感染症の予後は改善している。その反面，新たな副作用が明らかになり，リポジストロフィーもその一つである。そこで今回われわれは当科での現状について検討したので報告する。

対象・方法

抗HIV治療開始時にはリポジストロフィーを認めず，同一治療を1年以上継続したHIV感染者29名(平均年齢43.7歳，男性27名・女性2名)を対象とした。本人・医療者ともが特徴的体型変化を認識した場合にリポジストロフィーと診断した。リポジストロフィーの発症状況を調べ，その臨床病態を評価した。

結　果

リポジストロフィーと診断した症例は7名(24.1%)であった。年齢・性別・HIV感染リスク・HIV感染症病態には非リポジストロフィー症例と有意差を認めなかった。薬剤はリポジストロフィー症例でd4T・RTVの服用率が高く，これまでのすべての抗HIV治療期間が長い傾向を認めた。

リポジストロフィー症例では非リポジストロフィー症例と比較して治療前後で有意な体重減少が

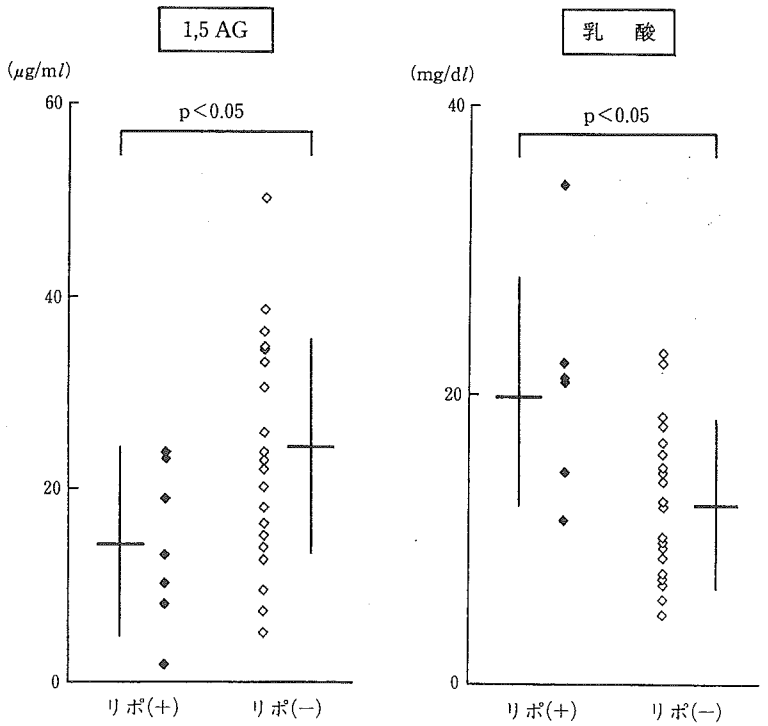

図1　リポジストロフィー症例と非リポジストロフィー症例における1,5アンヒドログルシトール(1,5 AG)値と乳酸値の比較

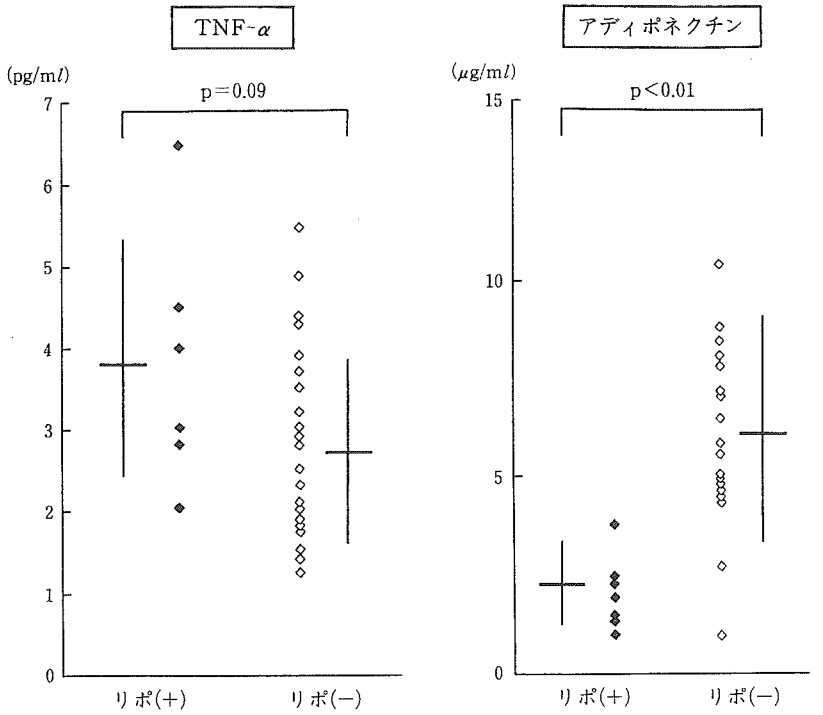

図2 リポジストロフィー症例と非リポジストロフィー症例におけるアディポサイトカイン(TNF-α・アディポネクチン)の比較

あり(p<0.01)，腹囲/臀囲比が有意に高値であった(p<0.01)。DXA(dual energy X-ray absorptiometry)で全身の脂肪分布を評価すると，体幹部/全身比はリポジストロフィー症例で61.2%，非リポジストロフィー症例で51.0%と有意差を認めた(p<0.01)。

治療後の脂質系検査をリポジストロフィー症例と非リポジストロフィー症例とで比較すると，それぞれの症例群で中性脂肪は327.0±106.7 mg/dl，230.5±146.2 mg/dl(p=0.06)，総コレステロールは231.3±44.5 mg/dl，183.3±48.9 mg/dl(p<0.05)，HDLコレステロールは44.9±16.7 mg/dl，39.5±9.6 mg/dl(p=0.3)であった。また，糖代謝の指標として1,5アンヒドログルシトール(1,5 AG)値を測定したところ，リポジストロフィー症例で有意に低値であり(p<0.05)，ミトコンドリア障害の指標と考えられる乳酸値はリポジストロフィー症例で有意に高値であった(p<0.05)(**図1**)。

脂肪組織から分泌される生物活性物質(アディポサイトカイン)に属するTNF-αとアディポネクチンの血清濃度をELISA法で測定した。リポジストロフィー症例でTNF-α値は高値の傾向があり(p=0.09)，アディポネクチン値は有意に低値であった(p<0.01)(**図2**)。

考　察

当科でのリポジストロフィーの発症率は欧米の報告に比べ低いものであったが，日本人HIV感染者にとっても重大な現象であることが示唆された。その発症は抗HIV治療と関連があり，特にd4TとRTVが重要な薬剤と考えられた。臨床的には体重変化と腹囲/臀囲比がリポジストロフィーの診断指標に役立つ可能性があり，DXAが客観的指標として利用できることが示された。リポジストロフィー症例では従来から指摘されているように脂質代謝異常・糖代謝異常・ミトコンドリア障害を認めた。また，リポジストロフィー症例では血清中TNF-α値・アディポネクチン値に