mg/m²の週1回4週投与群に8例の，計12例の再発・再燃B細胞リンパ腫患者が登録された。主な有害反応は，grade 2までの感冒様症状や発疹であり，多くは初回投与時に認められた。grade 4の血液毒性およびgrade 3以上の非血液毒性は1例も認められなかった。血中B細胞は初回投与2時間後にほぼ血中から消失したが，日和見感染は認められず，異種抗体は検出されなかった。適格11例中2例に完全奏効を，5例に部分奏効を認めた。リツキシマブの血中半減期は445±361 hoursと長く，投与を重ねるごとに血中濃度の上昇傾向を認めた。大半の患者において，投与開始3カ月の時点でリツキシマブが血中に検出可能であった。375 mg/m²の週1回4週投与は，わが国の再発・再燃B細胞リンパ腫患者にも安全かつ有効と結論した。

引き続き，再発・再燃低悪性度B細胞リンパ腫とマントル細胞リンパ腫を対象に第Ⅱ相試験が行われ，低悪性度B細胞リンパ腫適格61例中，完全奏効14例，部分奏効23例，全奏効割合61%という高い抗腫瘍効果が得られた。マントル細胞リンパ腫適格例の奏効割合は46%(6/13)であった[5]。

6．リツキシマブの将来性

再発・再燃低悪性度B細胞リンパ腫に対して，リツキシマブは単独で高い有効性を発揮することが判明した。骨髄毒性などの有害反応が軽度であることがリツキシマブの特長であり，適切な支持療法を行うことにより，外来投与可能である。

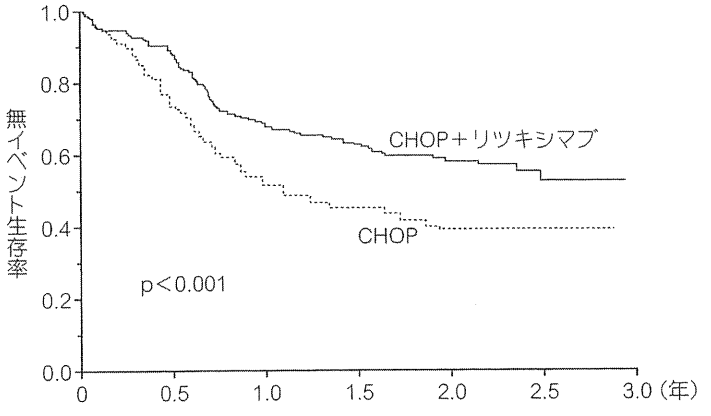
リツキシマブは，アポトーシスを誘導し，抗癌剤に耐性のBリンパ腫細胞株の薬剤感受性を増強することが確認された。骨髄毒性が軽度である点より，化学療法との併用が有望視された。米国で未治療例を主体とした低悪性度B細胞リンパ腫を対象に，CHOP療法（シクロホスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロン）とリツキシマブを併用した第Ⅱ相試験が行われた[6]。発現した有害反応の大半はCHOP療法による有害反応と考えられた。全奏効割合は95%（38/40）であり，うち22例が完全奏効に達した。

従来の化学療法では治癒しない進行期低悪性度B細胞リンパ腫患者に対し，リツキシマブと化学療法の併用は治癒をもたらすことが期待された。末梢血中や骨髄中の微少残存病変が高率に陰性化することにより，自家造血幹細胞移植のための*in vivo* purgingへの応用も期待された。

さらに，Coiffierらにより，再発・再燃中高悪性度B細胞リンパ腫に対するリツキシマブ単独投与の有効性（全奏効割合31%〔17/54〕）が報告され[7]，同様の結果はわが国の第Ⅱ相試験でも確認された。次いで，Voseらにより，未治療中高悪性度B細胞リンパ腫に対するCHOP療法とリツキシマブ併用の第Ⅱ相試験の優れた治療成績が発表された[8]。33例中31例が奏効し，20例（61%）に完全奏効が得られ，国際予後因子指標による高危険群18例における奏効割合は89%で，完全奏効率は56%であった。

2002年に，未治療高齢びまん性大細胞型B細胞リンパ腫（diffuse large B-cell lymphoma：DLBCL）を対象とした，リツキシマブとCHOP療法併用と，CHOP療法単独との第Ⅲ相試験の結果が報告された[9]。60～80歳，Ⅱ～Ⅳ期，PS（performance status）0～2のDLBCL症例を対象として，CHOP療法は標準量で3週毎に8コース実施され，リツキシマブ併用群ではCHOP療法実施と同日に375 mg/m^{2}のリツキシマブが点滴静注された。399例が登録され，リツキシマブ併用群に202例が，CHOP療法単独群に197例が割り付けられた。

観察期間中央値24カ月の時点における，原病増悪，再発もしくは死亡のイベント数は，リツキシマブ併用群で86（43%），CHOP療法単独群で120（61%）であった。リツキシマブ併用群の無イベント生存率（event-free survival：EFS）はCHOP療法単独群より有意に延長していた（$p < 0.001$）（図3）。国際予後因子指標による危険群別，70歳未満 vs. 70歳以上の年齢別のいずれの解析においても，リツキシマブ併用群のEFSが有意に上回った。完全奏効割合はリツキシマブ併用群で76%，CHOP療法単独群で63%（$p = 0.005$）であり，治療中の原病増悪の頻度はリツキシマブ併用群で9%，CHOP療法単独群で22%であった。リツキシマブ併用群の生存期間はCHOP療法単独群を有意に上回り（$p = 0.007$），2年生存割合は併用群で70%，CHOP単独群で57%であった。CHOP療法とリツキシマブの併用により，高齢DLBCL患者



No. AT Risk						
CHOP＋リツキシマブ	202	177	137	108	63	19
CHOP	197	144	101	72	42	17

図3 CHOP療法単独もしくはCHOP療法とリツキシマブ併用の両群に割り付けられた399例の無イベント生存率（EFS）

リツキシマブ併用群のEFSは，CHOP療法単独群より有意に延長している。

（文献9より）

における完全奏効割合，EFS と生存が改善されるが，毒性の有意な増加は認められないと結論された。

進行期 DLBCL に対する治療成績改善の努力は，新規抗癌剤開発，併用療法の組み合わせの検討，自家造血幹細胞移植併用による抗癌剤増量などに向けられてきたが，明らかな改善が得られなかった。従来の抗癌剤とは全く異なる作用機序を有する抗体療法の導入が，DLBCL の治療成績の打破につながったことは注目に値する。

わが国では，単剤の第Ⅰ相，第Ⅱ相試験に引き続き，未治療進行期低悪性度Ｂ細胞リンパ腫に対する CHOP 療法とリツキシマブを併用したランダム化第Ⅱ相試験（同時投与法と連続投与法を比較）が実施され，両投与法とも高い安全性・有効性を有することが判明した[10]。

おわりに

抗体療法は，多くの障害を乗り越えて，その臨床的有用性が確立された。悪性リンパ腫においては，Ｂ細胞リンパ腫に対するキメラ型抗 CD20 抗体と抗 CD20 radioimmunoconjugate[11] の研究が精力的に行われてきたが，カリケアマイシン抱合抗 CD22 抗体，次世代抗 CD20 抗体，抗 CD52 抗体などの開発が進められている。また，成人Ｔ細胞白血病リンパ腫を主な標的として抗 CCR4 抗体の臨床試験が活発に展開されており[12]，わが国から発せられる重要な新薬開発として注目されている。

（飛内 賢正）

文　献

1) Sievers EL, Larson RA, Stadtmauer EA, et al：Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. J Clin Oncol 19：3244-3254, 2001
2) Maloney DG, Liles TM, Czerwinski DK, et al：Phase clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Blood 84：2457-2466, 1994
3) McLaughlin P, Grillo-Lopez AJ, Link BK, et al：Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma：Half of patients respond to a four-dose treatment program. J Clin Oncol 16：2825-2833, 1998
4) Tobinai K, Kobayashi Y, Narabayashi M, et al：Feasibility and pharmacokinetic study of a chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in relapsed B-cell lymphoma. Ann Oncol 9：527-534, 1998
5) Igarashi T, Kobayashi Y, Ogura M, et al：Factors affecting toxicity, response and progression-free survival in relapsed patients with indolent B-cell lymphoma and mantle cell lymphoma treated with rituximab：Japanese phase Ⅱ study. Ann Oncol 13：928-943, 2002

6) Czuczman MS, Grillo-Lopez AJ, White CA, et al : Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 17 : 268-276, 1999
7) Coiffier B, Haioun C, Ketterer N, et al : Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma : A multicenter phase Ⅱ study. Blood 92 : 1927-1932, 1998
8) Vose JM, Link BK, Grossbard ML, et al : Phase Ⅱ study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. J Clin Oncol 19 : 389-397, 2001
9) Coiffier B, Lepage E, Briere J, et al : CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346 : 235-242, 2002
10) Tobinai K, Ogura M, Itoh K, et al : Randomized phase Ⅱ study of concurrent and sequential combinations of rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy in untreated indolent B-cell non-Hodgkin lymphoma: 7-year follow-up results. Cancer Sci 101 : 2579-2585, 2010
11) Witzig TE, White CA, Wiseman GA, et al : Phase Ⅰ/Ⅱ trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20$^+$ B-cell non-Hodgkin's lymphoma. J Clin Oncol 17 : 3793-3803, 1999
12) Yamamoto K, Utsunomiya A, Tobinai K, et al : Phase Ⅰ study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. J Clin Oncol 28 : 1591-1598, 2010

B細胞リンパ腫に有効な抗体療法
放射性物質がついた新薬も登場

悪性リンパ腫

あくせいりんぱしゅ

飛内賢正（とびないけんせい）医師
国立がん研究センター中央病院
副院長（研究担当）／
血液腫瘍科・造血幹細胞移植科長
東京都中央区築地5-1-1
☎03-3542-2511

血液がんの一つで、白血球の一種であるリンパ球ががん化するもの。年間約1万2千人が発症と、血液がんの中で患者数がいちばん多い。近年は薬物療法の進歩により、治癒も期待できるようになっている。

埼玉県在住の主婦・香川良子さん（仮名・64歳）は、8年前にわきの下のリンパ節（イラスト参照）が腫れているのに気づき、近くの病院で検査してもらったところ、「濾胞性リンパ腫」と診断された。これはリンパ球のうち、成熟B細胞ががん化したものだ。

血液のがんは、悪性リンパ腫、白血病、多発性骨髄腫の三つに大別される。このうち、もっとも患者数が多いのが悪性リンパ腫だ。血液中のリンパ球ががん化し、リンパ節に腫瘤をつくる。リンパ節以外にも胃や小腸、肺、脳、目、鼻などに腫れができることもある（これらを節外性リンパ腫と呼ぶ）。

リンパ球には、B細胞、T細胞、NK（ナチュラルキラー）細胞の3種類がある。それぞれの細胞が前駆細胞や成熟細胞の段階でがん化することがあるため、悪性リンパ腫には頻度の低いものまで含めると30種類以上もある（イラスト参照）。

悪性リンパ腫は、その組織型から「ホジキンリンパ腫」と、それ以外の「非ホジキンリンパ腫」に分けられる。日本人に多いのは非ホジキンリンパ腫で、さらにその約7～8割をB細胞リンパ腫が占める。

近年、このB細胞リンパ腫だけに作用する分子標的薬（抗体療法）が登場し、標準治療が大きく変わった。

悪性リンパ腫は病気の進行の速さによって、「低悪性度」「中悪性度」「高悪性度」の三つに分類され（204ページ表参照）、それぞれに応じた治療法がある。低悪性度の場合は進行が遅いため、すぐに治療を始めずに経過を観察し、必要になった段階で治療開始という選択もある。

抗がん剤と併用で治療効果がアップ

香川さんのリンパ腫は低悪性度だったが、検査でわきの下以外にもリンパ節の腫れが見つかり、抗がん剤治療を受けることになった。

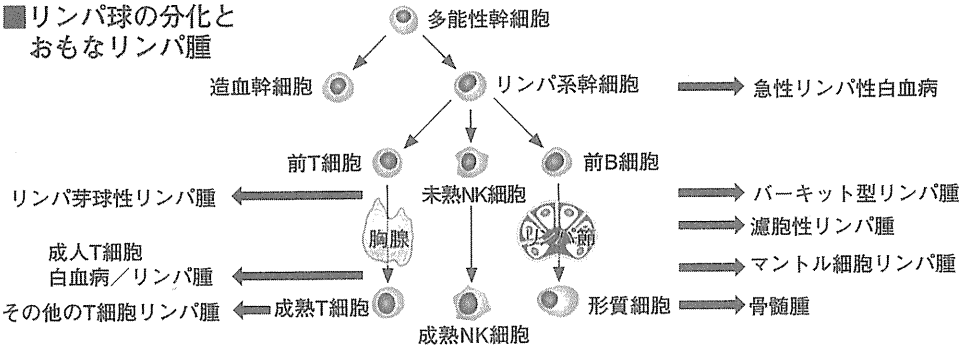
当時、濾胞性リンパ腫治療の第一選択の一つとされていたのが「CHOP療法」だ。抗がん剤の「シクロホスファミド」「ドキソルビシン」「ビンクリスチン」とステロイド薬の「プレドニゾロン」を組み合わせて使用する。

香川さんは一時的によくなったが、2年後に再発。2001年に承認された抗がん剤「リツキシマブ」を投与する治療を受けるために国立がん研究センター中央病院血液腫瘍科に紹介された。同院副院長の飛内賢正医師は言う。

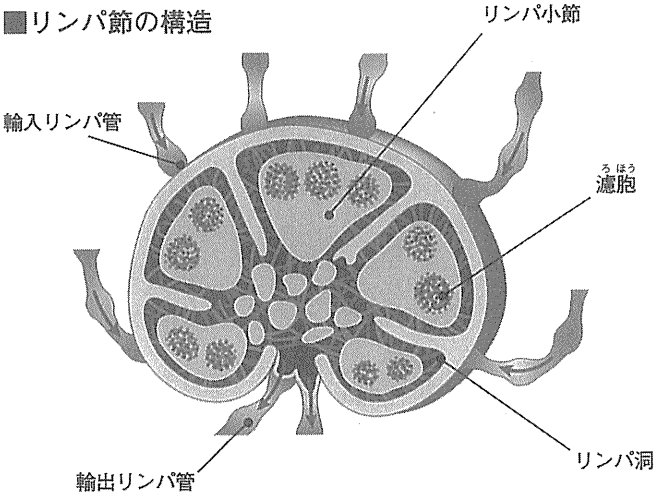
「リツキシマブは、各種がんで開発されている分子標的薬の先駆けとなった画期的な抗体医薬で、悪性リンパ腫の治療に大きな進歩をもたらしました。もともとは濾胞性リンパ腫の患者さん用に開発された薬で、濾胞性リンパ腫など低悪性度B細胞リンパ腫の再発患者さんに投与すると5～6割の人に効果があります」

リツキシマブは、もともと人間の体に備わっている「抗原抗体反応」という免疫の仕組みを利用した薬剤だ。B細胞だけにある「CD20」というたんぱく

■リンパ球の分化とおもなリンパ腫



■リンパ節の構造



質（抗原）に結合し、抗原抗体反応によってNK細胞やマクロファージなどの免疫担当細胞を活性化するなどして、がん細胞を攻撃する。飛内医師はこう説明する。

「リツキシマブの利点は、B細胞だけを狙い撃ちすること。ほかの細胞への影響が少なくてすむのです。CD20は大半のB細胞がもっているので、B細胞リンパ腫のほとんどの患者さんにリツキシマブを使うことができます」

リツキシマブは点滴薬で外来治療が可能。ただ、副作用は少ないが、ないわけではないので、初回は入院して受けるほうが確実だ。1回の点滴時間は3～4時間。単剤で使用する場合は通常、1週間に1回で、4～8週続ける。

「典型的な副作用が点滴投与時の免疫反応です。点滴後1日以内に発熱や寒気、皮膚のプツプツやかゆみなどがみられることがありますが、しばらくするとおさまります」（飛内医師）

香川さんもCD20陽性であることがわかり、この治療を受けた。いったんはよく効き、その後3年ほどは

■悪性度による分類

	悪性度	B細胞性	NK／T細胞性
低悪性度	年単位でゆっくり進行するタイプ。おだやかで症状も起こしにくいので、病気と付き合っていく治療がメーン。	●濾胞性リンパ腫 ●MALTリンパ腫 ●小細胞性リンパ腫 ●形質細胞リンパ腫	●菌状息肉腫 皮膚が赤らんだり、湿疹ができたりと多様な症状を起こす
中悪性度	月単位で進行する。実際にはさまざまな性質の病気があることから、「中～高悪性度」と表現することもある。	●マントル細胞リンパ腫 ●濾胞性リンパ腫 ●びまん性大細胞型リンパ腫	●末梢T細胞リンパ腫 ●血管免疫芽球型リンパ腫 ●鼻型NK／T細胞リンパ腫 ●未分化大細胞リンパ腫
高悪性度	見つかり次第、強力な治療が必要な、非常に進行が速いタイプ。病状は週単位で変化していく。	●リンパ芽球性リンパ腫 ●バーキットリンパ腫	●リンパ芽球性リンパ腫 ●成人T細胞白血病リンパ腫（急性型）

病気の進行の速さによって三つに分類され、それぞれに応じた治療法がある

名医のセカンドオピニオン

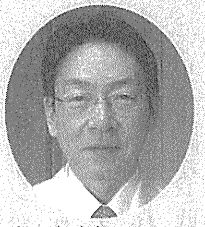
放射線療法や造血幹細胞移植も

悪性リンパ腫はわかりにくい病気といわれることが多い。その理由を、独立行政法人国立病院機構・名古屋医療センター院長の堀田知光医師はこう説明する。

「一つには、固形がんと違って全身のいたるところから発生し、症状も多様であるためです。さらに病気のタイプも多く、それによって治療法も異なってくるからでしょう。適切な治療を受けるためには、患者さんもこの病気について正しく理解することが大切です」

堀田医師によると、悪性リンパ腫の特徴の一つは、悪性度にかなり違いがあること。進行が遅くて放置してもすぐには問題にならないものから、ただちに治療しないと命にかかわるものまで、非常に幅広い。

「つまり、治療方針を決めるためには、病気の広がりや悪性度などを見極めることが大事なのです」（堀田医師）



ほった ともみつ
堀田知光医師
独立行政法人国立病院機構
名古屋医療センター
院長
名古屋市中区三の丸4-1-1
☎052-951-1111

ホジキンリンパ腫は首のリンパ節からわきの下のリンパ節、脾臓（ひぞう）というように連続して順番に病巣が広がっていくのが特徴。この場合は病巣の広がりを示す病期を重視する。一方、非ホジキンリンパ腫は病巣の広がり方が連続性とは限らないので、悪性度や組織型を目安にすることが多いという。

タイプ別の治療方針を紹介してもらうと――。

●ホジキンリンパ腫

一つの領域のリンパ節にがん

再発しなかった。

「リツキシマブは現在、中悪性度のびまん性大細胞型B細胞リンパ腫を含むすべてのB細胞リンパ腫にも保険適用になっています。また、初発の患者さんにCHOP療法にリツキシマブを併用した『R-CHOP療法』をすると、CHOP療法だけよりも治癒率が15～20%アップすることが複数の大規模臨床試験で確認され、びまん性大細胞型B細胞リンパ腫ではすでにR-CHOP療法が標準治療になっています」（同）

新薬も続々登場 T細胞リンパ腫にも

悪性リンパ腫の治療薬は次々と開発されている。すでに国内臨床試験が終わり、08年に認可されたのが、CD20に結合する「ゼヴァリン」という新薬だ。これは、リツキシマブの元となる抗体に放射性物質をくっつけたもの。この抗体が結合した腫瘍性B細胞と、隣接する腫瘍性B細胞に放射線を照射することができる。

「米国の臨床試験では、リツキシマブが効かなくなった低悪性度B細胞リンパ腫患者の約7割に有効と報告されています。リツキシマブと異なり、1回投与でいいこともメリットです」

と、飛内医師も評価する。ただ、ゼヴァリンには次のようなマイナス面がある。

▼放射性物質をつけた抗体が骨髄に入ることで白血球や血小板に対する影響がある。骨髄毒性があるために、原則として従来の抗がん剤とは併用できない。

▼効果が期待できるのは低悪性度にとどまっている場合で、中悪性度の場合はあまり効果が期待できない。

▼放射性物質を扱うための設備と核医学の専門家の協力が必要。現状では限られた施設でしか受けられない。

香川さんはリツキシマブでの治療後、また再発。

ちょうどゼヴァリンの臨床試験をしているときだったので、それに参加した。一度、白血球が減少して再入院しただけで、5年間再発していないという。

「低悪性度B細胞リンパ腫は再発しやすいのが問題ですが、近年、治療の選択肢が増えました。患者さんにとっては朗報でしょう」（同）

さらに、B細胞表面にあるCD22を標的にした抗体薬の研究も進んでいる。

一方、B細胞系のリンパ腫に比べて一般的に化学療法の効きが悪いとされるT細胞系のリンパ腫だが、待望の新薬「ネララビン」が07年12月に薬価基準に収載された。治療可能となるのは、再発または難治性のT細胞性急性リンパ性白血病とT細胞性リンパ芽球性リンパ腫。これは悪性リンパ腫と急性白血病の境界領域の疾患で、小児や若い男性に多いのが特徴だ。

「患者数は多くありませんが、再発すると治りにくいのが問題です。この薬は日本では臨床試験が完全に終了していませんが、未承認薬使用問題検討会議からの推奨や患者会の要望もあって、先行して実施された国外データをもとに承認されました。国外との承認の時間差『ドラッグ・ラグ』が問題になっている今、新しい流れをつくったという点でも注目されます」（同）

また、九州、沖縄地方に住んでいる人に多い成人T細胞白血病リンパ腫に対する抗体薬も日本で開発されている。臨床試験で有望な結果が得られており、早期の承認が期待されている。

ライター・石井典子

がとどまっている限局型には、化学療法4コース＋放射線療法。病期が進んだ場合は化学療法を6～8コース。化学療法は、「ドキソルビシン（アドリアマイシン）」「ブレオマイシン」「ビンブラスチン」「ダカルバジン」の4剤を組み合わせた「ABVD療法」が標準的。

●B細胞リンパ腫

中・高悪性度の限局型は化学療法（CHOP療法）＋放射線療法。やや進行したものでは、本文でも取り上げたリツキシマブを併用するR-CHOP療法。低悪性度の場合、従来は経過観察だったが、今はR-CHOP療法で生命予後もよくなっている。

●T細胞リンパ腫

CHOP療法が基本だが、化学療法だけで治療がむずかしいときは、造血幹細胞移植も視野に入れる。

「悪性リンパ腫はここ20～30年で治療法がもっとも進歩したがんであり、治療体系も整っています。最初に受ける治療が肝心なので、納得できないときはセカンドオピニオンを上手に利用してください」（同）

60

Adult T-cell Leukemia/Lymphoma

Keiji Iwatsuki

Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Summary

Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell malignancy caused by human T-cell leukemia virus type 1 (HTLV-1). ATLL occurs in certain endemic areas of HTLV-1 infection, including Asia. The discovery of ATLL and HTLV-1 has not only contributed tremendously to the understanding of the pathogenesis of virus-induced neoplasms but also provided new insights into anthropology though retrovirus research. This review includes the clinicopathologic features of ATLL and the molecular pathogenesis induced by HTLV-1 infection.

Introduction

In 1976, Takatsuki and his colleagues reported, for the first time, an unusual peripheral mature T-cell leukemia which they designated adult T-cell leukemia (ATL). They reported that the majority of ATL patients were born in the Kyushu area, the southwestern part of Japan[1]. Miyoshi et al. established T-cell lines such as MT-1 and MT-2 from blood samples from ATL patients, using cocultivation with cord blood lymphocytes as a feeder[2]. Interestingly, chromosomal analysis demonstrated that some of the established T-cell lines were not derived from the ATL patients, but from the cord blood cells. Hinuma et al discovered the presence of serum antibodies directed against MT-1 cells in all ATL patients and some inhabitants in the Kyushu area, and postulated the involvement of a specific pathogen associated with ATL cells[3]. Although no viral particles were found in ATL cells *in vivo* by electron microscopy, virus-like particles were detected in the cell line cells. Using a molecular approach, Yoshida et al. clearly demonstrated that the virus-like particles were retroviruses containing reverse transcriptase activity, and that the T-cell lines harbored a proviral DNA sequence integrated in the host genome[4]. In addition to the common retrovirus structure of 'LTR-gag-pol-env-LTR', the newly isolated retrovirus, designated ATL virus (ATLV) in Japan, contained a unique pX sequence, resulting in a genome structure of 'LTR-gag-pol-env-pX-LTR'. Independent of the discovery of ATLV by Japanese researchers, Gallo and his colleagues isolated a retrovirus from a T-cell line, HUT102, established from a Caribbean patient with mycosis fungoides, who should actually have been diagnosed as having ATL in line with the present disease entity[5]. Retroviruses isolated from a Japanese group and an American group were later demonstrated to be essentially the same at the sequence level and designated as human T-cell leukemia virus type 1 or human T-cell lymphotropic virus type 1 (HTLV-1)[6].

Adult T-cell leukemia/lymphoma (ATLL), encompassing both leukemic and lymphomatous stages, is a peripheral T-cell malignancy caused by HTLV-1, but its infection alone is not sufficient to develop ATLL.

Epidemiology of ATLL

A sero-epidemiological survey by Tajima et al demonstrated that HTLV-1 infections are prevalent in Japanese,

Correspondence to: Keiji Iwatsuki
Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
E-mail: keijiiwa@cc.okayama-u.ac.jp

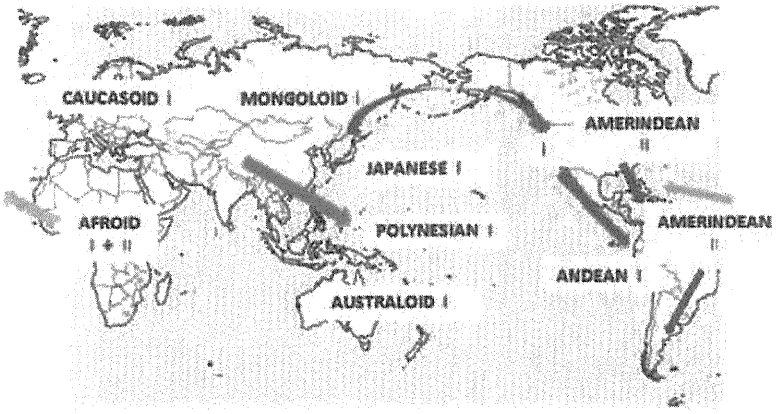


Fig. 1. Migration of ancient HTLV-1 carriers (Ref 7. with modification).

native Andeans, Iranians, Central Africans, and African descendants in the Caribbean Basin and South America[7]. It is intriguing to note that extremely low incidences of seropositivity and ATLL were found in Korea and Eastern China, neighboring countries of Japan. Recent studies of HTLV-1 phylogeny on the LTR genome sequence showed that HTLV-1 could be classified into three major lineages, designated the Melanesian, Central African, and Cosmopolitan lineages. The Cosmopolitan lineage can be further divided into the Transcontinental, Japanese, West African, and North African subgroups[8]. HTLV-1 proviral genome sequences obtained from 1,500-year-old Andean mummies showed a similar lineage of HTLV-1 sequences to those of Japanese ATLL patients, which revealed that Asian Mongolians carrying HTLV-1 moved to the Andes at least 1,500 years ago (Fig. 1).

The male to female ratio of ATLL patients is approximately 1.5:1[9]. The cumulative incidence of ATLL is estimated to be 2.5-5% among HTLV-1 carriers in Japan, and the age of disease onset ranged from the 20s to the 80s, with an average of 58 years.

Clinical Features and HTLV-1-associated Disorders

Based on the hematological findings, blood chemistry results, and organ involvements, Shimoyama et al classified ATLL into acute, chronic, lymphomatous, and smoldering types[10]. More than 50% of ATLL patients present with cutaneous lesions that included disseminated papules, nodules, and tumors. Scaly erythemic plaques and erythroderma indistinguishable from those of mycosis fungoides and Sézary syndrome occur in some patients (Fig. 2).

HTLV-1 carriers are often associated with virus-related complications, including HTLV-1-associated myelopathy /tropical spastic paraparesis (HAM/TSP)[11,12], uveitis, HTLV-1-assocuated arthropathy (HAAP), and Sjögren's syndrome. The incidence of HAM/TSP is low in Japanese as compared with that in the Chilean mestizo population, probably because of a genetic immunological background against HTLV-1 as described below. HTLV-1-associated 'infectious dermatitis' observed in the Caribbean Basin has not been seen in Japan.

Histopathology, Immunophenotype, and Cytology

The presence of atypical T-cells with convoluted or lobulated nuclei, so-called 'flower cells', is a hematological hallmark of ATLL, although the number of such cells varies among subtypes. Tumor cells express a mature T-cell phenotype of CD2+, CD3+, CD4+, and CD5+. Most ATLL cells are negative for CD8, CD7, and CD26. A few cases express CD8, or both CD4 and CD8. CD30 is also expressed by anaplastic cells. The strong expression of CD25 (IL2Rα) is a striking feature of ATLL[13]. ATLL cells usually express regulatory T-cell (Treg) markers such as CCR4 and FoxP3, although their function is still controversial.

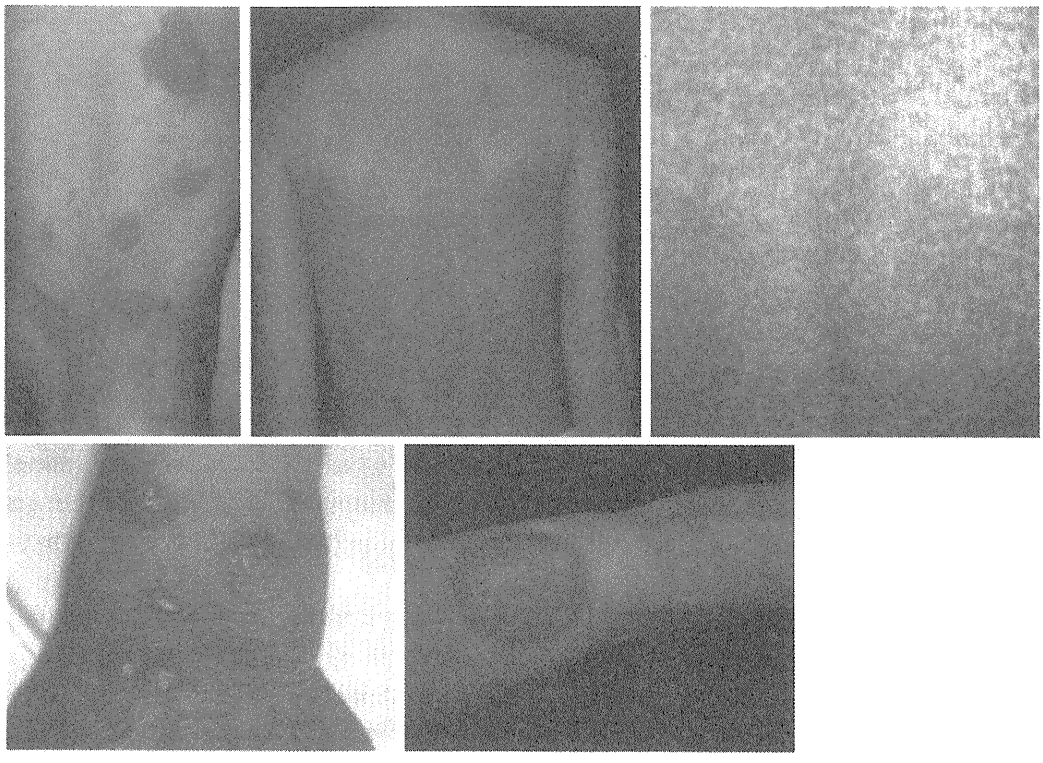


Fig. 2. Cutaneous features of ATLL.

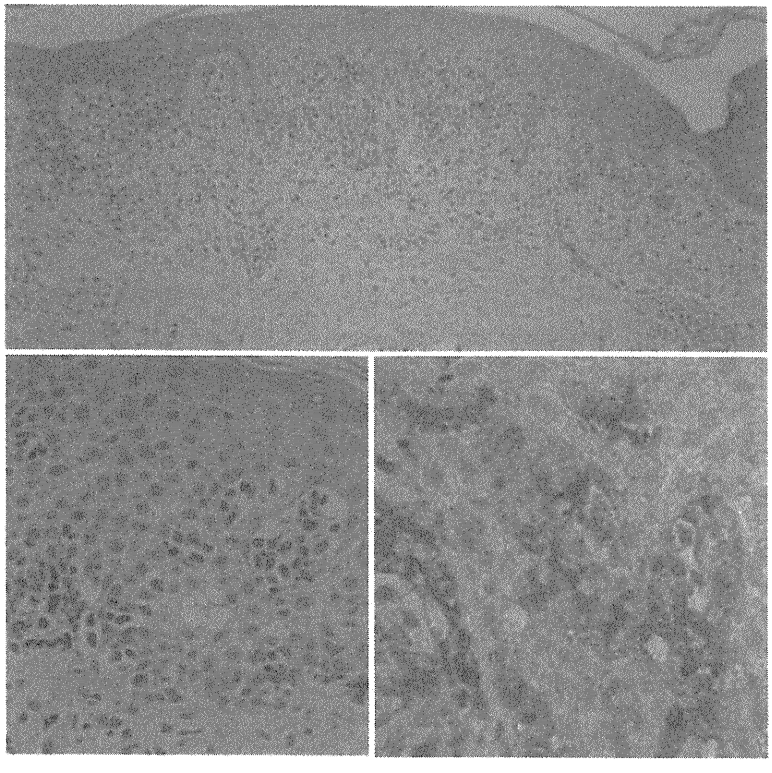


Fig. 3. HTLV-1 proviral sequence and functions of a *pX* gene product, Tax.

Neoplastic lymphocytes of ATLL in the lymph nodes and other organs may exhibit a pleomorphic appearance referred to as pleomorphic small, medium and large cell types, anaplastic, and angioimmunoblastic T-cell lymphoma-like variants. Cutaneous ATLL lesions frequently show epidermotropic infiltration of atypical lymphocytes with Pautrier's microabscess formation indistinguishable from that of mycosis fungoides (Fig. 3). Perivascular infiltrates containing atypical lymphoid cells are common in ATLL, and strong expression of CD25 suggests the possibility of ATLL rather than mycosis fungoides.

HTLV-1 viral particles are usually not detected in circulating neoplastic cells, but they are visible in cultured ATLL cells (Fig. 4). Karyotypic abnormalities revealed frequent gains at 1q, 2p, 3p, 4q, 7p, and 7q, and losses of 10p, 13q, 16q, and 18p[14].

Diagnostic Procedures

A serological test for anti-HTLV-1 antibody is essential in screening examinations for ATLL. The presence of anti-HTLV-1 antibody is not sufficient for the diagnosis of ATLL, because HTLV-1 carriers may present with T-cell lymphomas other than ATLL. To confirm the diagnosis of ATLL, clinicians should use Southern blotting or reversed PCR methods to identify monoclonal integration of HTLV-1 proviral DNA. Integration of a deleted form of proviral DNA is detected in one-third of ATLL patients, which

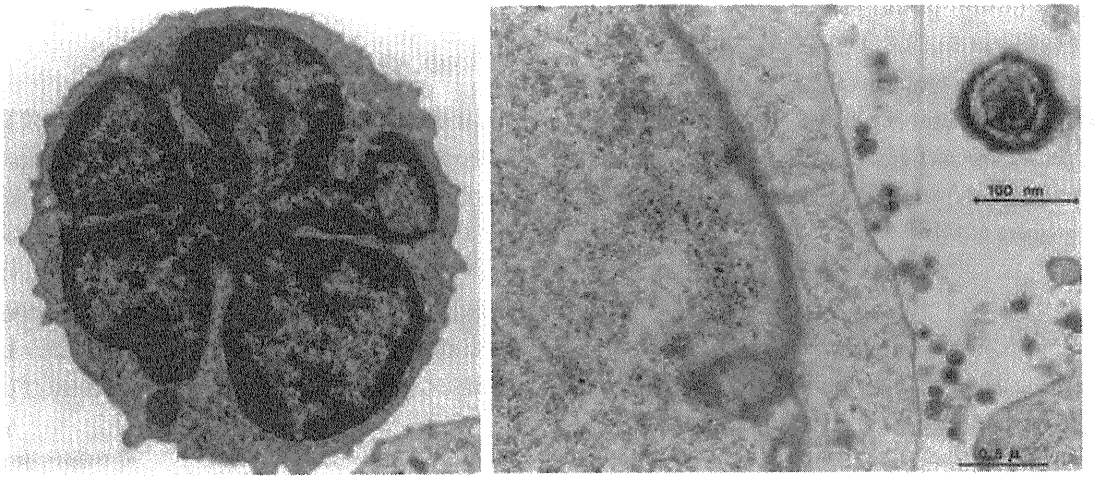


Fig. 4. Epidermotropic infiltration of ATLL cells forming Pautrier's microabscesses indistinguishable from those of mycosis fungoides. The tumor cells express IL-2R α (CD25) (lower right).

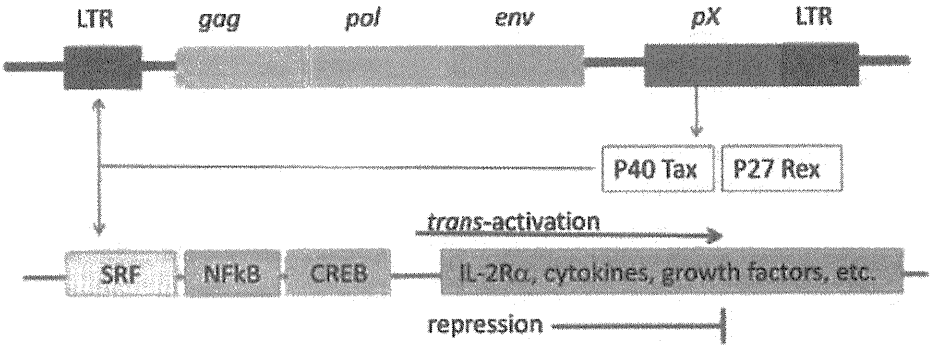


Fig. 5. Circulating ATLL cells show 'flower cell' appearance. HTLV-1 virions are observed in cultured ATLL cells, but can hardly been detected in freshly isolated ATLL cells.

might be associated with clinical subtypes and prognosis.

Molecular Pathogenesis

In the development of ATLL, there has been no evidence of a 'viral oncogene' or 'insertional activation' mechanism. A unique HTLV-1 sequence, pX, encodes three proteins: p40-Tax, p27-Rex, and p21. Tax is a *trans*-activator of the viral genome, and Rex suppresses splicing of the viral transcripts[15]. Many investigators have focused on the transcriptional activation and repression of cellular genes by p40- Tax protein[16]. Tax binds enhancer-binding proteins such as NF-κB and cyclicAMP responsive element binding protein (CREB), and transcriptional cofactors such as p300/CBP (CREB binding protein), thereby enhancing transcriptional signals to generate IL2Rα and other cytokines (Fig. 5). On the other hand, Tax inhibits tumor suppressor proteins such as $p16^{INK4}$ and $p15^{INK4}$. Since Tax is not always expressed in ATLL cells, additional oncogenic molecules including HTLV-1 bZIP factor (HBZ) and mutations of the cellular genes might be involved in development of ATLL[17].

Progression and Prognostic Factors

Approximately 5% of HTLV-1 carriers may develop ATLL or HTLV-1-associated disorders in a 50-year clinical observation. In other words, the remaining 95% of HTLV-1 carriers do not experience any HTLV-1-related disorders during their lifetime, even though they continue to harbor HTLV-1-infected T-cells (Fig. 6). The immunogenetic background of an HTLV carrier was found to be associated with the development of ATLL. In Japanese, HLA-A*26, B*4002, B*4006, and B*4801 alleles predispose persons to develop ATLL, probably because of limited recognition of the Tax epitopes with the subsequent impairment generating the Tax-specific, CD8+ cytotoxic T-lymphocytes (CTLs)[18]. The expression of Tax proteins seems to be essential for the initial step of transformation, but Tax-positive cells might be targeted by host CTLs. Many ATLL cells, therefore, lack Tax expression, which allows them to evade the host CTL response, and the cells require further oncogenic molecules such as HBZ or mutations of tumor suppressor genes. In an overt leukemic stage, mutation or deletion of p53 or $p16^{INK4}$/$p15^{INK4}$ is observed in approximately 50% of ATLL patients.

Prevention of HTLV-1 Infections

Three major HTLV-1 infection routes have been proven: 1) blood transfusion from HTLV-1 carriers, 2) breast feeding, and 3) sexual transmission, mainly from males to females. At the present time, the prevention of HTLV-1 infection has been carried out in Japan by a serological screening test for HTLV-1 among blood donors and pregnant women, and refraining from breast feeding by HTLV-1 carriers[19].

Treatments

Treatments should be chosen based on the ATLL subtypes and patients' conditions. Recommended polychemotherapy for acute and lymphomatous types includes the vincristine, cyclophosphamide, doxorubicin, and prednisolone (VCAP), doxorubicin, ranimustine, and prednisolone (AMP), and vincristine, etoposide, carboplatin, and prednisolone (VEMP) regimens. The VCAP, AMP, or VEMP regimen might be superior to biweekly CHOP. A

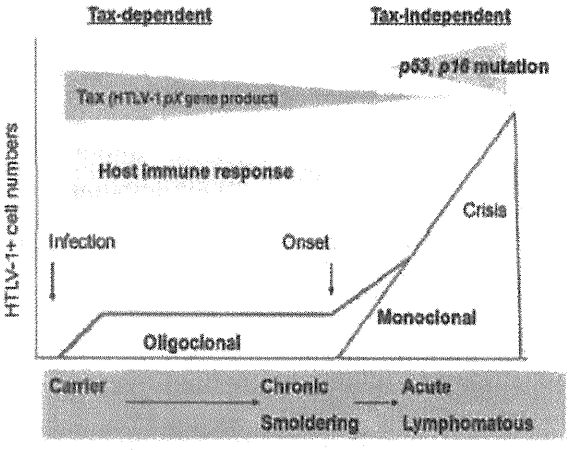


Fig. 6. Natural history of HTLV-1 carriers. Tax is a key molecule in the early stage of ATLL, but further genomic or karyotypic alterations are observed in neoplastic cells of overt ATLL. During the progression of the illness, various HTLV-1-associated complications may occur.

combination treatment with interferon-α and zidovudine (AZT) might result in favorable response rates particularly in acute, chronic, and smoldering types of ATL[14]. *Allo*-hematopoietic stem cell transplant (HSCT) is a possible option for young patients with aggressive ATLL, but it remains to be answered which protocol of *allo*-HSCT is suitable for ATLL.

References

1. Uchiyama T, Yodoi J, Sagawa K, et al. Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood 1977;50:481-492.
2. Miyoshi I, Kubonishi I, Yoshimoto S, et al. Type C virus particles in a cord T-cell line derived by co-cultivating normal human cord leukocytes and human leukaemic T cells. Nature 1981;294:770-771.
3. Hinuma Y, Nagata K, Hanaoka M, et al. Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. Proc Natl Acad Sci U S A 1981;78:6476-6480.
4. Yoshida M, Miyoshi I, Hinuma Y. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc Natl Acad Sci U S A 1982;79:2031-2035.
5. Poiesz BJ, Ruscetti FW, Gazdar AF, et al. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci U S A 1980;77:7415-7419.
6. Watanabe T, Seiki M, Yoshida M. HTLV type I (U. S. isolate) and ATLV (Japanese isolate) are the same species of human retrovirus. Virology 1984;133:238-241.
7. Tajima K, Takezaki T. Ethnoepidemiology of ATL/HTLV in Mongoloids with special reference to Mongoloid dispersal. Gann Monogr Cancer Res 2003;50:277-288.
8. Li HC, Fujiyoshi T, Lou H, et al. The presence of ancient human T-cell lymphotropic virus type I provirus DNA in an Andean mummy. Nat Med 1999;5:1428-1432.
9. Ohshima K, Jaffe ES, Kikuchi M. Adult T-cell leukemia/lymphoma. In: Swerdlow SH, et al (eds) WHO classification of tumours of haematopoietic and lymphoid tissues. IARC, Lyon, 2008, pp 281-288.
10. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol 1991;79:428-437.
11. Osame M, Usuku K, Izumo S, et al. HTLV-I associated myelopathy, a new clinical entity. Lancet 1986;1:1031-1032.
12. Gessain A, Barin F, Vernant JC, et al. Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. Lancet 1985;2:407-410.
13. Uchiyama T, Hori T, Tsudo M, et al. Interleukin-2 receptor (Tac antigen) expressed on adult T cell leukemia cells. J Clin Invest 1985;76:446-453.
14. Tsukasaki K, Hermine O, Bazarbachi A, et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. J Clin Oncol 2009;27:453-459.
15. Seiki M, Hattori S, Hirayama Y, et al. Human adult T-cell leukemia virus: complete nucleotide sequence of the provirus genome integrated in leukemia cell DNA. Proc Natl Acad Sci U S A 1983;80:3618-3622.
16. Suzuki T, Kitao S, Matsushime H, et al. HTLV-1 Tax protein interacts with cyclin-dependent kinase inhibitor p16INK4A and counteracts its inhibitory activity towards CDK4. EMBO J 1996;15:1607-1614.
17. Murata K, Hayashibara T, Sugahara K, et al. A novel alternative splicing isoform of human T-cell leukemia virus type 1 bZIP factor (HBZ-SI) targets distinct subnuclear localization. J Virol 2006;80:2495-2505.
18. Sonoda S, Yashiki S, Takahashi K, et al. Altered HLA antigens expressed on T and B lymphocytes of adult T-cell leukemia/lymphoma patients and their relatives. Int J Cancer 1987;40:629-634.
19. Hino S, Sugiyama H, Doi H, et al. Breaking the cycle of HTLV-I transmission via carrier mothers' milk. Lancet 1987;2:1158-159.

Int J Hematol (2011) 94:430–434
DOI 10.1007/s12185-011-0934-4

PROGRESS IN HEMATOLOGY

Memorial PIM: adult T-cell leukemia—from discovery to recent progress

Current status of HTLV-1 infection

Toshiki Watanabe

Received: 10 August 2011 / Revised: 31 August 2011 / Accepted: 2 September 2011 / Published online: 4 October 2011

Abstract It is 30 years since human T-cell leukemia virus type 1 (HTLV-1) was identified as the first human retrovirus. To assess the implications of the virus for human health it is very important to know the past and present prevalence. Most of the estimates of HTLV-1 prevalence are based on serological screening of blood donors, pregnant women and other selected population groups. The widely cited estimate that the number of HTLV-1 carriers in Japan is 1.2 million was calculated from data that are now more than 25 years old. Here I summarize previous reports of prevalence studies in the world and Japan. Then, a recent analysis of seroprevalence of healthy blood donors in Japan will be described in comparison with that of 1988. A decrease in the number of HTLV-1 carriers in Japan was demonstrated, however, it is still more than one million. The number has increased in the metropolitan areas, probably reflecting the migration of Japanese population. I conclude that there is a paucity of general population data in countries where HTLV-1 is endemic, and re-evaluation of HTLV-1 infection is required to understand the virus burden on the human health.

Keywords Seroprevalence of HTLV-1 · Vertical and horizontal transmission · Prevention of transmission

1 Introduction

Discovery of adult T-cell leukemia (ATL) by Takatsuki's group [1] was followed by the discovery of the first human retrovirus human T-cell leukemia virus (HTLV) and adult T-cell leukemia virus (ATLV) by research groups of the United State and Japan, respectively [2, 3]. In 1980, Poiesz et al. [2] identified HTLV in a T-cell line from a patient with cutaneous T-cell lymphoma. Independently of this, Hinuma and Miyoshi found specific antibodies against ATL cells in the patients' sera [3] and type C retrovirus particles produced by a T-cell line established from peripheral blood of ATL patient in 1981 [4]. In 1982, Yoshida et al. [5] identified ATLV as a human retrovirus. Soon, HTLV and ATLV were shown to be identical at the sequence level and were named HTLV type 1 (HTLV-1) [6, 7].

After the discovery of HTLV-1, related viruses have been isolated and HTLV is now composed of 4 related HTLVs, HTLV-1 to HTLV-4 [8]. However, only HTLV-1 has been convincingly linked to human diseases at present. HTLV-1 has six reported subtypes (subtypes A–F). Diverse studies have been performed on HTLV-1 subtyping but present a minor role in the epidemiological status of the virus. The great majority of infections are caused by the cosmopolitan subtype A, and there is no report of subtype influence on the pathogenic potential of HTLV-1 [9].

2 HTLV-1 infection in the world

Approximately 20 million people worldwide are estimated to be infected with HTLV-1 [10]. Among them, more than 90% remain asymptomatic carriers during their lives. Since 1986, HTLV-1 screening has been developed and was slowly implemented worldwide [11]. In 1993, HTLV-1 screening of blood donors was already performed in all developed countries and in many developing countries where HTLV-1 is endemic.

T. Watanabe (✉)
Department of Medical Genome Sciences,
Graduate School of Frontier Sciences, The University of Tokyo,
4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan
e-mail: tnabe@ims.u-tokyo.ac.jp

About the geographic distribution of the virus, a lot of studies have been done in these 30 years. Results indicate that Japan, Africa, the Caribbean islands, and Central and South America are the areas of highest prevalence in the world (reviewed in [12], [13]). However, the data from international prevalence studies should be interpreted and compared with caution as to the population selection criteria, because any difference in the diagnostic strategies can interfere with the final result. Data of the serological screening of healthy blood donors mainly provide basis for the estimation of the global prevalence of HTLV-1, which tends to underestimate the prevalence in the population. The geographic distribution of HTLV-1 infection is shown in Fig. 1 [13].

In addition to Japan, high rates of HTLV-1 infection have been reported for some Caribbean islands in studies of blood donors or segments of the general population. In Jamaica, the prevalence is around 5%. In Africa, the seroprevalence increases from the north to the south, varying from 0.6% in Morocco to greater than 5% in several sub-Saharan African countries, for example, Benin, Cameroon, and Guinea-Bissau, however, more studies are clearly required about these regions in detail. In Europe and North America, the prevalence is low and limited to groups that emigrated from endemic areas. For blood donors, very low rates were found in France (0.0039%) and the United States (0.025%). In South America, the virus was found in all countries, but more studies of the general population are needed to ascertain the real prevalence of HTLV-1. Medium prevalence was found in blood donors from Chile (0.73%) and Argentina (0.07%). In Australia, a prevalence of 14% was reported in a cluster among Aborigines in the Northern Territory, even though the prevalence in blood donors is low. The prevalence of HTLV-1 was highest in the two studies of Japanese islands (36.4%) and lowest in studies from Mongolia, Malaysia and India. In Haiti the prevalence was 3.8%; in Africa between 6.6 and 8.5% in Gabon, and 1.05% in Guinea. Only three studies were from West Africa and none were from the South; the only study from India was from the north of the country. It has to be

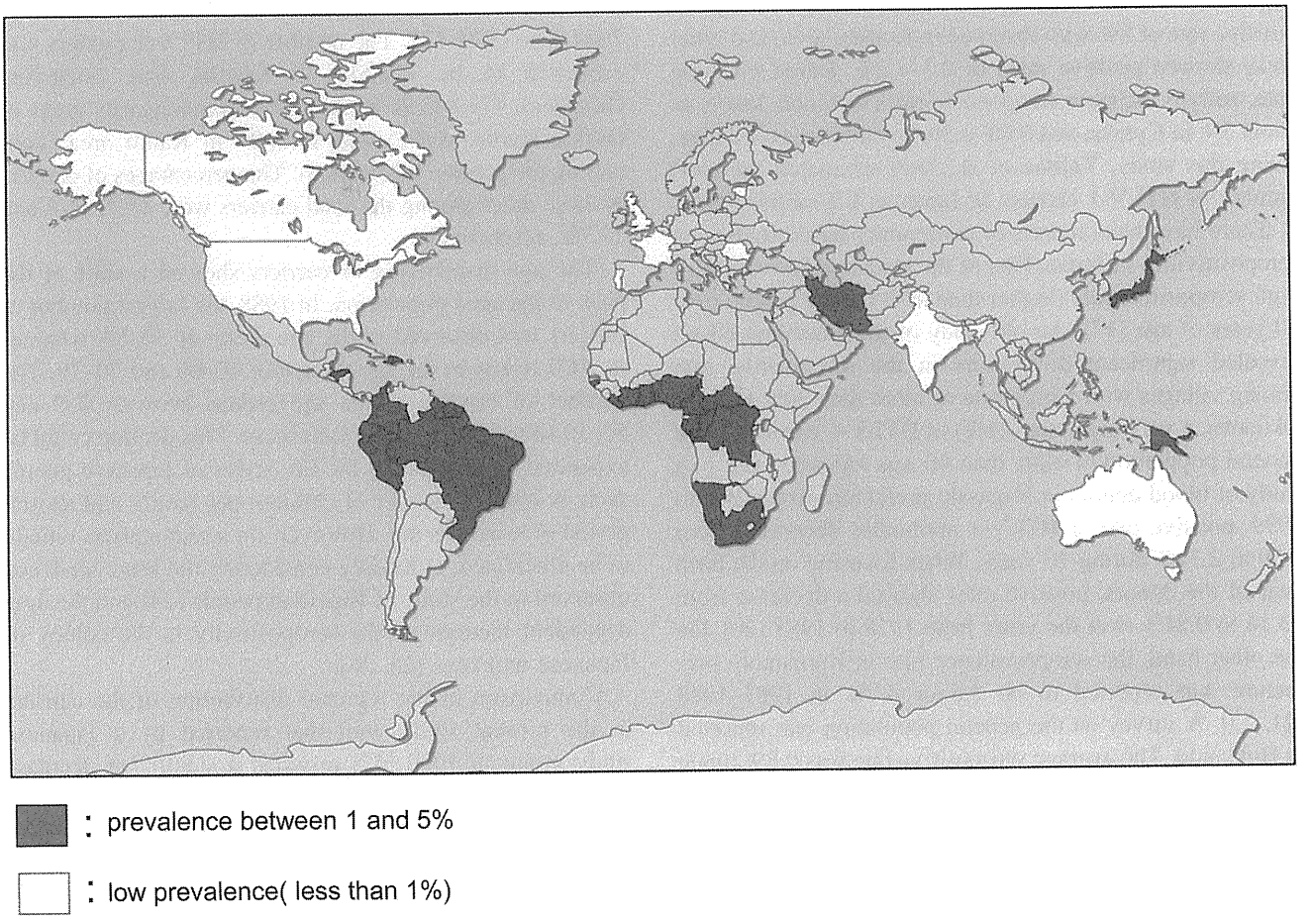


Fig. 1 Countries with endemic HTLV-I, defined as prevalence between 1 and 5% in some populations, are shown in *red*. Countries with reports of low prevalence (less than 1% in some groups), due mainly to immigration from endemic areas, are shown in *yellow*. It should be noted that HTLV-I endemic areas do not correspond exactly to the country boundaries shown in the map, for example, Brazil, Japan and Iran, where HTLV-I is limited to residents of certain areas of each country (modified from the reference [13])

concluded that there is a paucity of general population data from countries in which HTLV-1 is endemic, and that new studies are required to reevaluate the global burden of infection (reviewed in ref. [12] and [13]).

3 HTLV-1 Infection in Japan

3.1 Past studies of HTLV-1 carriers

Many efforts have been made to know the number of HTLV-1 carriers since the discovery of the virus in Japan. An example of early nationwide studies is the report of seropositive rates in the 15 blood centers of Japanese Red Cross [14]. It was reported that among 15 blood centers, 7 showed a higher positive rates between 6 and 30%, tested by indirect immunofluorescence assays (IFA). The other report is based on the data of all blood centers in Japan, which was the only study of all areas of Japan before the resent survey by Satake et al. [15]. They studied by IFA about 15,000 samples composed of 200 samples of blood donors aged from 40 to 64 from each center. The highest positive rate of 8% was observed in Kyushu area, and other areas showed positive rates of 0.3–1.2%. Based on these data, authors estimate seropositive rates of blood donors as about 3% in Kyushu and 0.08–0.3% in other areas of Japan. Using this study, Tajima et al., later estimated the total number of HTLV-1 carriers in Japan as 1.2 million [16].

There have been reports of community-based studies on seropositivities in Japan. One of the studies reported a very high seropositive rate (higher than 40%) in the people over 40 years of age [17]. An old study of the Tsushima Island revealed significant differences in the seropositive rate among villages with a high rate of more than 30% [18]. In Okinawa, a very high rate (21%) of HTLV-1 carriers in the general population of older than 40 was reported [19]. In a study of blood donors in Nagasaki prefecture from 1990 to 1999, positive rate of HTLV-1 antibodies decreased from 3.39 to 2.78% during 10 years. When focusing on the birth year of the donors, positive rates showed a decrease from 13.14 to 0.81% over the years from 1928 to 1983 [20]. On the other hand, the seroprevalence rate in Kumamoto prefecture was reported to be 3.6 or 4.7% in 1987–1988 [21, 22]. A survey on the general population was reported in Hokkaido. The average seropositive rate was 0.8% (male 0.6% and female 0.9%), with some regions showing higher seroprevalence rates as much as 5.2% [23].

Taken together, studies in 1980s and 1990s were mostly community-based ones using sera of blood donors. The oldest nationwide survey of the seroprevalence of HTLV-1 in blood donors and estimation of the number of HTLV-1 carriers [15, 16] had been referred to as the only published information until recently.

3.2 Recent studies of HTLV-1 infection in Japan

Based on the numbers of seropositive blood donors, Satake et al. have estimated the number of HTLV-1 carriers in Japan [15]. They analyzed data of blood donors who donated for the first time in 2006 and 2007, because Japanese Red Cross Blood center has notified the donors with the results of screening tests since 2000. This notification would have caused a bias in the population of total blood donors reducing the number of HTLV-1 carriers. In Satake's study, the total of number of tested was 1,196,321 (M: 704,074; F: 492,247), among them, HTLV-1 antibody was confirmed to be positive in 37,787 (M: 2,115; F: 1,672). Thus, the positive ratio was 0.32% for both male and female. Since the ages of blood donors were limited between 16 and 64, they estimated the seropositive rates of the peoples of younger than 15 or older than 65 by an assumption that the positive rate will increase exponentially in the young population, and for the aged people, by adding the average increase in the percentage in each age group in 20 years comparing with the data in 1988. Consequently, the estimated number of HTLV-1 carriers in 2007 was 1,078,722. The number of HTLV-1 carriers was estimated to be 492,582 in Kyushu area (including Okinawa), 171,843 in Kinki area (containing city areas of Osaka, Kyoto, Kobe) and 190,609 in Kanto area (containing the greater Tokyo area). The percentages of carriers in these areas among the total carriers were 45.7, 15.9 and 17.7%, respectively.

The age distribution of carriers showed a shift of the peak to the aged population. In 1988, the largest number of carriers was observed in the age group of 50–59, whereas in 2007 it was in the age groups of 60–69 and 70–79. The number of carriers in the age groups between 0–9 and 50–59 showed a significant decrease. This decline could be explained by changes in the life styles of Japanese people such as smaller number of children per family and shorter period of breast feeing. However, the exact reasons remain to be elucidated, especially considering the same tendency observed in the study of Brazilian people [24] and the age-dependent increase in the seropositivity in the colony of Japanese monkeys [25, 26].

Comparison of the regional distribution of the carriers in the present study with that reported by a Japanese study group in 1990 [27] revealed a significant decrease of the HTLV-1 carriers in Kyushu area (50.9 to 45.7%) and an increase in Kanto area (10.8 to 17.7%). The observed changes were considered to be mainly due to the migration of Japanese people from the Kyushu/Okinawa area to the metropolitan areas (Fig. 2). This interpretation is supported by the observation of Uchimaru et al. [28], who studied HTLV-1 carriers in Tokyo area and revealed that many of HTLV-1 carriers in Tokyo are either born in

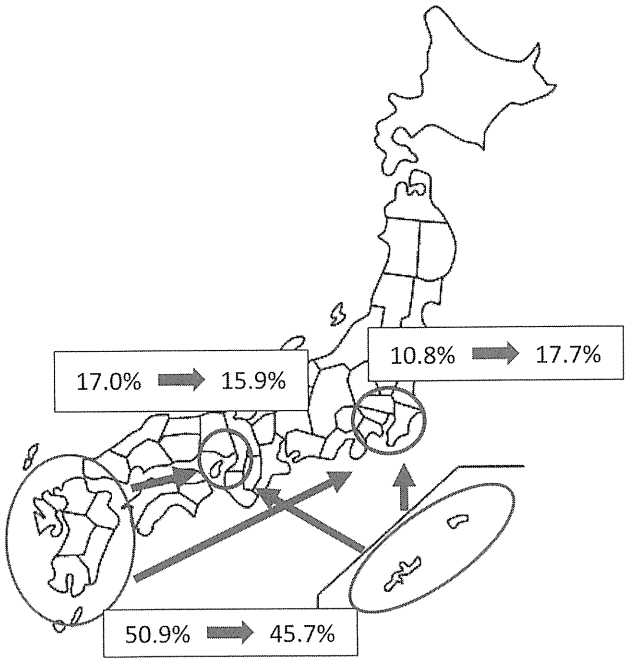


Fig. 2 Distribution of HTLV-1 carriers in Japan. Migration to the metropolitan areas is apparent. The number of HTLV-1 carriers in the endemic areas is still the largest, however, those in the great Tokyo area is significantly increasing

the endemic areas or the descendants of migrants from those areas.

4 Remaining problems and future directions

We have attributed the decrease in the HTLV-1 prevalence in Japan to the modernization and westernization of life styles of Japanese people. However, when we consider the same tendency in Brazil and age-dependent increase of seropositive rates in Japanese monkeys, we have to be cautious about interpretation of the observed data and may have to re-evaluate the meaning of the age-dependent carrier rates.

Another point that was raised by Satake's study is unexpectedly high increase in the positive rates in 20 years in the age-cohort [15]. This indicates the presence of horizontal transmission of the virus, probably through sexual contacts. This mode of infection should have contributed, at least to some extent, to the age-dependent increase in the positive rates. Thus, epidemiological studies on the horizontal transmission are definitely required; however, no such studies are now under way in Japan.

Taken together, we have to realize that we do not have enough data about the prevalence of HTLV-1 even in Japan, where serological data of blood donors are the only information to estimate the prevalence. Serological screening of the pregnant women that started in 2011 will provide valuable information about young females in Japan. Since the number of carriers who develop ATL is estimated about 1,200 per year in Japan, we have to expect more than 20,000 ATL patients from the present carriers in the future. In addition to the screening for the blood donors, prevention of mother-to-child infection by stopping breast feeding will greatly reduce the vertical transmission, nonetheless, there still remain other modalities of HTLV-1 infection, that are sexual transmission and possible trans-uterine infection. Neutralizing antibodies are often observed in carriers of HTLV-1 [29–32]. Furthermore, previous reports suggest that a primed immune response can be protective or prevent infection postviral exposure and challenge. It was shown that maternally acquired antibody protect infants from HTLV-1 infection in the early months of life [33]. A vaccine candidate based on an envelope expressing vaccinia virus provides protection to experimentally challenged primates [34, 35], and an attenuated viral strain provides long-term protection against the closely related bovine leukemia virus [36]. Taking all these into consideration, a costeffective vaccine may be a viable objective for prophylactic intervention in HTLV-1-endemic areas.

References

1. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood. 1977;50:481–92.
2. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA. 1980;77:7415–9.
3. Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto T, Kinoshita KI, et al. Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. Proc Natl Acad Sci USA. 1981;78:6476–80.
4. Miyoshi I, Kubonishi I, Yoshimoto S, Akagi T, Ohtsuki Y, Shiraishi Y, et al. Type C virus particles in a cord T-cell line derived by co-cultivating normal human cord leukocytes and human leukaemic T cells. Nature. 1981;294:770–1.
5. Yoshida M, Miyoshi I, Hinuma Y. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc Natl Acad Sci USA. 1982;79:2031–5.
6. Watanabe T, Seiki M, Yoshida M. Retrovirus terminology. Science. 1983;222:1178.
7. Gallo RC. History of the discoveries of the first human retroviruses: HTLV-1 and HTLV-2. Oncogene. 2005;24:5626–930.
8. Mahieux R, Gessain A. The human HTLV-3 and HTLV-4 retroviruses: new members of the HTLV family. Pathol Biol (Paris). 2009;57:161–6.
9. Ono A, Miura T, Araki S, Yamaguchi K, Takatsuki K, Mori S, et al. Subtype analysis of HTLV-1 in patients with HTLV-1 uveitis. Jpn J Cancer Res. 1994;85:767–70.

10. de Thé G, Kazanji M. An HTLV-I/II vaccine: from animal models to clinical trials? J Acquir Immune Defic Syndr Hum Retrovirol. 1996;13(Suppl 1):S191–8.
11. Inaba S, Sato H, Okochi K, Fukada K, Takakura F, Tokunaga K, et al. Prevention of transmission of human T lymphotropic virus type 1 (HTLV-1) through transfusion, by donor screening with antibody to the virus. One-year experience. Transfusion. 1989;29: 7–11.
12. Goncalves DU, Proietti FA, Ribas JGR, Araujo MG, Pinheiro SR, Guedes AC, et al. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. Clin Microbiol Rev. 2010;23:577–89.
13. Proietti FA, Anna Bárbara, Carneiro-Proietti F, Bernadette C, Catalan-Soares, Murphy EL, et al. Global epidemiology of HTLV-I infection and associated diseases. Oncogene. 2005;24: 6058–68.
14. Hinuma Y, Komoda H, Chosa T, Kondo T, Kohakura M, Takenaka T, et al. Antibodies to adult T-cell leukemia-virus-associated antigen (ATLA) in sera from patients with ATL and controls in Japan: a nation-wide sero-epidemiologic study. Int J Cancer. 1982;29:631–5.
15. Satake M, Yamaguchi K. Annual report of the group study for survey of HTLV-1 infection and HTLV-1 related diseases in Japan. 2009 (in Japanese) (Manuscript submitted).
16. Tajima K. The 4th nation-wide study of adult T-cell leukemia/lymphoma (ATL) in Japan: estimates of risk of ATL and its geographical and clinical features. The T- and B-cell Malignancy Study Group. Int J Cancer. 1990;45:237–43.
17. Kohakura M, Nakada K, Yonahara M, Komoda H, Imai J, Hinuma Y. Seroepidemiology of the human retrovirus (HTLV/ATLV) in Okinawa where adult T-cell leukemia is highly endemic. Jpn J Cancer Res. 1986;77:21–3.
18. Tajima K, Kamura S, Ito S, Ito M, Nagatomo M, Kinoshita K, Ikeda S. Epidemiological features of HTLV-I carriers and incidence of ATL in an ATL-endemic island: a report of the community-based co-operative study in Tsushima, Japan. Int J Cancer. 1987;40:741–6.
19. Kohakura M, Nakada K, Yonahara M, Komoda H, Imai J, Hinuma Y. Seroepidemiology of the human retrovirus (HTLV/ATLV) in Okinawa where adult T-cell leukemia is highly endemic. Jpn J Cancer Res. 1986;77:21–3.
20. Chiyoda S, Kinoshita K, Egawa S, Inoue J, Watanabe K, Ifuku M. Decline in the positive rate of human T-lymphotropic virus type-1 (HTLV-1) antibodies among blood donors in Nagasaki. Intern Med. 2001;40:14–7.
21. Lee SY, Mastushita K, Machida J, Tajiri M, Yamaguchi K, Takatsuki K. Human T-cell leukemia virus type I infection in hemodialysis patients. Cancer. 1987;60:1474–8.
22. Iida S, Fujiyama S, Yoshida K, Morishita T, Shibata J, Sato T, et al. The seroprevalence of anti-HTLV-1 antibodies in patients with various liver diseases. Hepatogastroenterol. 1988;35:242–4.
23. Kwon KW, Yano M, Sekiguchi S, Iwanaga M, Fujiwara S, Oikawa O, et al. Prevalence of human T-cell leukemia virus type 1 (HTLV-I) in general inhabitants in non-adult T-cell leukemia (ATL)-endemic Hokkaido, Japan. In Vivo. 1994;8:1011–4.
24. Barcellos NT, Fuchs SC, Mondini LG, Murphy EL. Human T lymphotropic virus type I/II infection: prevalence and risk factors in individuals testing for HIV in counseling centers from Southern Brazil. Sex Transm Dis. 2006;33:302–6.
25. Ishida T, Yamamoto K, Kaneko R, Tokita E, Hinuma Y. Seroepidemiological study of antibodies to adult T-cell leukemia virus-associated antigen (ATLA) in free-ranging Japanese monkeys (Macaca fuscata). Microbiol Immunol. 1983;27:297–301.
26. Hayami M, Komuro A, Nozawa K, Shotake T, Ishikawa K, Yamamoto K, et al. Prevalence of antibody to adult T-cell leukemia virus-associated antigens (ATLA) in Japanese monkeys and other non-human primates. Int J Cancer. 1984;33:179–83.
27. Tajima K, Itoh S, Itoh T, Kinoshita K, Shimotohno K. Epidemiology of ATL and HTLV-1. In: the annual report of the group study "Inhibition of mother-to-child infection and ATL" (1990). 1991 (in Japanese).
28. Uchimaru K, Nakamura Y, Tojo A, Watanabe T, Yamaguchi K. Factors predisposing to HTLV-1 infection in residents of the greater Tokyo area. Int J Hematol. 2008;88:565–70.
29. Astier-Gin T, Portail JP, Londos-Gagliardi D, Moynet D, Blanchard S, Dalibart R, et al. Neutralizing activity and antibody reactivity toward immunogenic regions of the human T cell leukemia virus type I surface glycoprotein in sera of infected patients with different clinical states. J Infect Dis. 1997;175:716–9.
30. Londos-Gagliardi D, Armengaud MH, Freund F, Dalibart R, Moze E, Huet S, et al. Antibodies directed against a variable and neutralizable region of the HTLV-I envelope surface glycoprotein. Leukemia. 1997;11(Suppl. 3):38–41.
31. Hadlock KG, Rowe J, Perkins S, Bradshaw P, Song GY, Cheng C, et al. Neutralizing human monoclonal antibodies to conformational epitopes of human T-cell lymphotropic virus type 1 and 2 gp46. J Virol. 1997;71:5828–40.
32. Hadlock KG, Rowe J, Foung SK. The humoral immune response to human T-cell lymphotropic virus type 1 envelope glycoprotein gp46 is directed primarily against conformational epitopes. J Virol. 1999;73:1205–12.
33. Takahashi K, Takezaki T, Oki T, Kawakami K, Yahiski S, Fujiyoshi T, et al. Inhibitory effect of maternal antibody on mother-to-child transmission of human T-lymphotropic virus type I. Int J Cancer. 1991;49:673–7.
34. Kazanji M, Heraud JM, Merien F, Pique C, de The G, Gessain A, Jacobson S, et al. Chimeric peptide vaccine composed of B- and T-cell epitopes of human T-cell leukemia virus type 1 induces humoral and cellular immune responses and reduces the proviral load in immunized squirrel monkeys (*Saimiri sciureus*). J Gen Virol. 2006;87:1331–7.
35. Kazanji M, Tartaglia J, Franchini G, de Thoisy B, Talarmin A, Contamin H, Gessain A, de The G, et al. Immunogenicity and protective efficacy of recombinant human T-cell leukemia/lymphoma virus type 1 NYVAC and naked DNA vaccine candidates in squirrel monkeys (*Saimiri sciureus*). J Virol. 2001;75:5939–48.
36. Kerkhofs P, Gatot JS, Knapen K, Mammerickx M, Burny A, Portetelle D, Willems L, Kettmann R. Long-term protection against bovine leukaemia virus replication in cattle and sheep. J Gen Virol. 2000;81:957–63.

特集　成人 T 細胞白血病（ATL）

1．日本における HTLV-Ⅰ/ATL 研究，対策の歴史，現状

渡邉　俊樹
Watanabe　Toshiki

東京大学大学院 新領域創成科学研究科 病態医療科学分野 教授

Summary　1970 年代から始まる前史に続く 1977 年の ATL 疾患概念の提唱により，我が国の ATL 研究がスタートした。その後，日沼，三好，吉田らの研究によって，ヒトで初のレトロウイルスの同定と，ATL の原因ウイルスとしての確立が成された。1980 年代の熱気にあふれた時期を過ぎて，1990 年代には研究支援の低下と研究活動の低迷期を迎え，2000 年前後には現状に対する危機感が広がった。その後の臨床家，研究者，および患者・キャリアの団体の活動が，2010 年 12 月の菅 前首相による「HTLV-Ⅰ総合対策」の策定へとつながった。

はじめに
ATL 発見に至る歴史

1970 年代は免疫学の進歩により，リンパ球を T 細胞と B 細胞に区別する事が可能になった。これを受け，欧米の血液学研究者はリンパ系悪性腫瘍細胞の T，B 分類の作業を進め始めた。この流れを受けて，我が国でも 1970 年代には，T 細胞性慢性リンパ球性白血病（T-CLL）に関するいくつかの興味深い症例報告がなされている[1~3]。つまり，西南日本に予後不良の悪性リンパ腫が多い事，悪性リンパ腫の家族内発症が見られる事，Hodgkin 病が南九州に多い事，本来稀な疾患であるセザリー症候群や皮膚型 T 細胞リンパ腫（CTCL）の症例報告が九州地方に多い事などの記載がある。さらに，リンパ腫から白血化して短期間で死亡する例が少なくない事，末梢血に核の分葉した奇妙な白血病細胞が出現する事などが記載されている。

さらに，悪性リンパ腫を T 細胞と B 細胞の表面マーカーで分類すると，T 細胞性の割合が我が国では欧米に比べて異常に高いこと，ホジキン病と診断された症例の中で 10 ～ 50% も T 細胞性リンパ腫が含まれることが明らかになった。これらの症例の大多数が，現在の概念では ATL と考えられる。したがって，ATL の疾患概念が提唱される以前から，多数の患者がいた事は明らかである。

高月らは，成人の T 細胞性の白血病の臨床的特徴を取りまとめ，国際学会で報告した。この報告内容は，現在の ATL に関する臨床的特徴をほぼ

T-CLL（T 細胞性慢性リンパ球性白血病）　CTCL（皮膚型 T 細胞リンパ腫）