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H. 知的財産権の出願・登録状況
（予定を含む）

1. 特許取得
該当なし

2. 実用新案登録
該当なし

3. その他
該当なし

血液内科医・皮膚科医のための統合 ATL 診療ガイドライン解説書案 2014

1. はじめに

1.1 血液内科と皮膚科の ATL 診療ガイドラインを踏まえて作成された本解説書の目的と使い方

ATL 診療ガイドラインは、血液内科と皮膚科の専門医向けにそれぞれ日本血液学会と日本皮膚科学会・日本皮膚悪性腫瘍学会で編集された①②③。その背景としては、1980 年代の全国調査では ATL 患者の 49%が皮膚病変を有し、今まで急性型やリンパ腫型など全身性に浸潤した ATL に対しては主に血液内科医が診療を行い、一方病変が皮膚に限局する ATL に対しては光線療法などの局所療法を主に皮膚科医が診療を行ってきた実態がある④。

この両科の ATL 診療ガイドラインに従い、全国で等しく ATL の診療が行われることが理想である。しかし日本全国での ATL 診療の均てん化を目指すとき、他の腫瘍に比べ本疾患は地域偏在性が著しく、加えて血液内科医と皮膚科医が連携してあるいは別々に個々の患者の診療にあたることがあるため、困難を感じざるをえない。すなわち専門医や医療機関の偏在等の問題があり、上記の両科ごとの診療ガイドラインのみでは不十分なケースが考えられる。具体的には、HTLV-1 キャリアが多く、ATL の症例数も多い九州地区の離島などで、血液内科医や皮膚科医以外の一般医師が ATL を診療しなければならない場合が想定される。血液内科医が ATL の皮膚病変を診療しなければならない場合、逆に、皮膚科医が急性型、リンパ腫型や慢性型など、皮膚以外の病変を伴った ATL を診療しなければならない場合も想定される。さらには、ATL の十分な診療経験がない血液内科医/皮膚科医が ATL 患者の診療にあたらなければならない場合もこれに当てはまるであろう。このような、両科の診療ガイドラインでは充足しない側面を補うことを目的に、血液内科医・皮膚科医のための統合 ATL 診療ガイドライン解説書として本書を作成した。

今回、厚生労働科学研究費補助金（H23-がん臨床-一般-022）「ATL の診療実態・指針の分析による診療体制の整備」班で、皮膚病変を有する ATL についての診療・研究のコンセンサスを論文化したこと⑤を踏まえ、両科に共通する部分の診療ガイドラインについて、それぞれのガイドライン作成に関わっている分担研究者を中心に、その解説書を作成した。血液内科医、皮膚科医がそれぞれ自らの診療科向けに作られた診療ガイドラインを参考にするのは当然のことであるが、双方向性に、血液内科医が皮膚科の、そして皮膚科医が血液内科のガイドラインを参考にして、お互いの科で ATL に対してどのような診療が行われているかを全国で等しく知ることができるようにも、この解説書を活用していただければ幸いである。

皮膚病変を有する ATL の診療の基本はもちろん血液内科・皮膚科の各診療ガイドライン

であることは言うまでもないが、ガイドラインを成書に例えれば、それらを紐解く際の参考資料として、この解説書を活用していただければ幸いである。。

ATL の病態・病型によって主に診療を担当する診療科は当然異なるが、両診療科が設置されている医療機関では、皮膚病変を有する ATL 患者の診療に際しては、原則として両診療科が併診すべきである。その際、それぞれの科の医師が他科のガイドラインを参照するにあたっても、この解説書を活用していただければ幸いである。

2. Clinical Question

2.1. 両科の役割分担

ここでは皮膚病変を有する ATL 患者を診療する際の、血液内科医と皮膚科医の役割分担について述べる。内容は血液内科医と皮膚科医が連携して診療を進められる医療環境を念頭に述べたものであり、どちらかが不在、あるいは両者とも不在の場合はそれ以外の医師が担当することもあり得る。

皮膚病変を有する ATL 患者を診療する際には、まず下山分類によって ATL の病型を確定する③。このための作業は血液内科の協力が得られる環境であれば、リンパ節生検（外科へ依頼）など適宜必要な全身の精査を血液内科が主体で診断を進める。頭頸部から骨盤部までの CT または PET/CT と上部消化管内視鏡検査は、病型診断に有用である。皮膚病変が ATL の病変であることを確認するために皮膚科医が皮膚生検をおこない、免疫組織学的な病理診断、さらには可及的に十分量の検体を採取することにより HTLV-1 プロウイルスのサザンブロット法（保険適用外）による ATL の診断を行う。皮膚悪性腫瘍ガイドラインでは「末梢血中の ATL 細胞が 5%未満で，皮膚型またはくすぶり型以外の臨床型に属さないもの」を暫定的に，「皮膚のみに病変を有する ATL」として扱っている①②。また、皮膚科医による皮疹型の確定も予後にかかわるため重要である⑤。

治療に関しては、詳細は両科の診療ガイドラインを参照されたいが、基本方針として、皮膚病変のある急性型・リンパ腫型、予後不良因子を持つ慢性型は、血液内科的な全身的治療と皮膚科的な皮膚局所の治療を合わせて行う。皮膚病変のあるくすぶり型、予後不良因子を持たない慢性型は，皮膚科的な局所治療を行い、内科的には他病変の出現、LDH、Ca と Alb 値について慎重に経過観察する。

2.2. 紹介のタイミング

2.2.1. ATL の病状変化に関連して

2.2.1.1. 当初に皮膚科医が主に診療している場合

皮膚科医が血液内科にコンサルトできる環境にあれば、患者を紹介するタイミングは大きく分けて二つあると考えられる。

1）皮膚の症候で皮膚科を受診した新患患者において ATL を疑った場合、原則として血液内科に紹介し、前項で述べたように下山分類をもとにした ATL の診断、病型の確定を依頼する。そこで皮膚病変のある急性型、リンパ腫型、予後不良因子を持つ慢性型と診断されればそのまま血液内科で全身的な治療を開始するとともに、皮膚科的な局所的治療を併用する。全身的な化学療法により通常は皮膚病変も寛解となるので、その後は血液内科単独の診療となりうる。しかし皮膚病変が結節腫瘤型などの場合は、化学療法後に残存することが少なくなく、一部は潰瘍形成や感染症併発によって治療開始前よりも病状が悪化する。このような重篤な場合は、両科が密に協力し血液内科医による全身管理と皮膚科医による皮膚病変管理を行うことが必要となる。一旦寛解となった後に、治療開始前とは異なるタイプの皮膚病変で再発することもあるので，何か変化があれば速やか皮膚科医に相談する必要がある。一方で、皮膚病変のあるくすぶり型、予後不良因子を持たない慢性型と診断されれば，皮膚科に戻り皮膚局所療法を行う。この場合は、内科も併診し他臓器病変の出現、LDH、Ca と Alb 値について慎重に経過観察することが推奨される。

2）皮膚病変を有するくすぶり型および予後不良因子を持たない慢性型の ATL を皮膚科単独で診療する場合、皮膚治療と合わせて経過観察を行い、下山分類に照らして急性型、リンパ腫型、予後不良因子を持つ慢性型への進行を疑われる場合には全身化学療法等の適応について再度血液内科へ紹介することとなる。下山分類ではくすぶり型または予後不良因子を持たない慢性型のままであるが皮膚病変が悪化するため、単剤経口抗がん剤または多剤併用抗がん剤療法を開始するかどうか検討する際にも、皮膚科と血液内科で治療方針について相談することが望ましい。

2.2.1.2. 当初に血液内科医が主に診療している場合

血液内科医が皮膚科にコンサルトを考える状況としても、前項と同様に二つの状況が考えられる。一つめは ATL を疑う新患患者を、診断・病型分類の結果、皮膚病変のあるくすぶり型もしくは予後不良因子を持たない慢性型と診断した場合である。通常、末梢血と肺に病変がないくすぶり型は、上記の診断には皮膚生検が必要である。従って皮膚の他に病変がなく、上記の病型を疑う場合には、速やかに皮膚生検を依頼する。そして生検の結果、ATL の皮膚病変と診断されればそのまま皮膚科での診療も継続する。また、二つめは一つめのケースと重なる部分もあるが、急性型やリンパ腫型、予後不良因子を持つ慢性型と診断した際に皮膚病変を伴っている場合、あるいはそれらの病型の ATL に対して診療を行っ

ている際に皮膚に何らかの病変をきたした場合である。ATL の皮膚病変、あるいは次項で触れる治療による皮膚合併症、またはそれら以外の皮膚疾患の鑑別のために皮膚科医にコンサルトし、必要に応じて皮膚生検等による診断と治療を受けることとなる。

2.2.2. 治療に伴う皮膚有害事象に関連して

2.2.2.1. ATL に対する治療後の皮膚合併症

前項までで述べた血液内科での全身化学療法中に、皮膚に何らかの病変をきたすケースは多い。ATL の皮膚病変や、免疫抑制状態を背景とした皮膚感染症など別の皮膚疾患も多くみられるなか、それらと同じくらい高頻度でみられるのが、薬物療法に伴う薬疹であり、治療薬の種々の抗がん剤のほか種々の抗菌剤、その他の薬剤が原因となる。予防的に用いられることも多いアロプリノール、ST 合剤などはしばしば原因となる。ATL の皮膚病変との鑑別には、皮疹の性状、ATL の他病変・腫瘍マーカー、薬剤歴などを総合的に評価するが、皮膚生検も含めて皮膚科が主体となって、血液内科も連携して診療に当たり、原因薬/被疑薬の中止を含めて検討する。

2.2.2.2. Mogamulizumab などによる皮膚合併症

ケモカイン受容体 CCR4 陽性で再発・難治の ATL に保険適用のある抗 CCR4 抗体（mogamulizumab）の高頻度な有害反応として薬疹がある⑥。Mogamulizumab の薬効から、ATL 細胞のみならず皮膚において CCR4 陽性の制御性 T 細胞も除去してしまうために、免疫反応が過剰に活性化して薬疹を生ずると考えられており、使用中のみならず、終了から数か月後の発症も報告されている。その重症度に応じて、速やかに mogamulizumab の中止とステロイドの局所・全身治療を行うことが推奨される。一方で、本剤が奏効した患者では奏効しなかった患者に比べてこの皮疹が多く観察されている。Mogamulizumab による薬疹は、休薬後も遷延・増悪する場合があることや、粘膜障害等の全身症状を伴い重篤化する場合があることが報告されており、皮膚生検による早期の確定診断と適時の治療介入が必要である。

2.2.2.3. 合併する感染症対策

ATL では細胞性免疫能が低下しているため、また抗がん剤やステロイド治療などのため、感染症を併発しやすい。皮膚感染症としては種々の真菌感染症と帯状疱疹が、全身感染症としては種々の細菌、真菌、ウイルス、ニューモシスチス感染症が高頻度である。皮膚に腫瘤性病変がある場合、特に抗がん剤などが奏効したのちに生じる潰瘍性病変は、好中球減少を伴って難治性の細菌感染症などを生じやすいので、両科の併診が望ましい。抗がん剤・抗体による治療中は真菌、ニューモシスチス感染症の予防が、造血幹細胞移植時にはさらにヘルペスウイルス感染症の予防が勧められている。くすぶり型・慢性型 ATL 患者が日和見感染症を発症した後に急性転化することが報告されており、経過観察には注意を要

する。

2.3. 定期フォローのタイミング

ATL 患者の定期フォローの間隔については、様々なケースがあるため一概には言えないものの、大別すると、血液内科・皮膚科の両科でそれぞれ全身化学療法や光線療法などのATL に対する治療を行っている場合と、無治療で経過観察を行っている場合の二つがある。

前者の場合には、入院あるいは外来での治療に分けられるが、毎日の診療が可能な入院治療は別として、外来での治療においても、化学療法のレジメンや光線療法の照射スケジュールなど、個々の症例での治療計画に基づいた適切な診療のタイミングがあると考えられ、ここでは詳述しない。

後者の、急性転化まで無治療での経過観察は、くすぶり型、予後不良因子を持たない慢性型ATL の標準診療とみなされている。しかし 5 年及び 15 年生存割合はそれぞれ約 50%、15%と長期予後は不良であり、病勢進行の有無を確認するためにはあまり経過観察間隔を長くすべきではないと考えられる③。一方、全く増悪の兆候がない症例に対しては、小刻みな通院を漫然と続けることは患者自身はもちろん、医療側にも負担となることに考慮すべきであろう。インドレント ATL の生存曲線は下に凸であること、特にくすぶり型が予後不良因子を持たない慢性型に比べて早期に病勢進行するとの報告もあることから、診断から 1 年程度は、くすぶり型であっても当初は 1 か月ごとに数か月、その後は数か月ごとに、診察、白血球数、リンパ系細胞総数（ATL 細胞を含む）、ATL 細胞比率、LDH、Ca、可溶性 IL2 受容体値をフォローすることは、診療における選択肢の 1 つであると考えられる。

2.4. 他科の治療をどこまで行うか、他院へ紹介する場合はどのようにするか。

2.4.1. 血液内科医が処方する皮膚局所療法

それぞれの診療科でどのような治療を行うかについては、基本的には 2.1 や 2.2 で述べたものが基本となる。しかし血液内科医が皮膚科医の協力を得られにくい環境で、皮膚のみに病変を有する ATL 患者を診療しなければならない場合も想定される。そのような場合でもまずは 2.2.1.2 で述べたように皮膚生検による診断が必須と考えられ、一度は皮膚科医に診断を依頼する。その後、可能であれば皮膚科医との連携をとりながら、あるいは皮膚科の診療ガイドラインを参照しながら皮膚病変の診療を行うとともに、血液内科の診療ガイドラインを参照しながら他病変の出現、LDH、Ca と Alb 値について慎重に経過観察する。効果判定についても皮膚科医の指導を受けるのが望ましいと考えられる。治療の内容として、単剤化学療法やインターフェロンγ療法などは血液内科的な治療の範疇にも入ると考えられるが、紫外線療法などの皮膚科特有な治療については、やはり小刻みな皮膚科医の指導が必須であり、基本的には皮膚科医の協力が得られる環境でのみ行われるべきと考えられる。

2.4.2. 皮膚科医が処方する全身抗がん剤、抗体医薬

逆に皮膚科医が、血液内科医の協力を得られにくい環境で、皮膚病変を有する急性型、リンパ腫型、予後不良因子を持つ慢性型 ATL 患者を診療しなければならない場合も想定される。そのようなケースでも、2.2.1.1 で述べたように、血液内科医の協力のもと、まずは適切な病型診断を行うことが必須である。そのうえで治療方針を相談のうえ決定し、合併症や年齢のため同種造血幹細胞移植の適応外と判断された場合は、単剤から、ときに多剤併用の化学療法、抗体療法を皮膚科医が行うこととなる。特に，悪性リンパ腫や ATL の治療経験が少ない皮膚科の施設においては，治療に際して血液内科医との密接な連携をとり，様々な合併症や治療効果判定についても相談が必要である。これらは本来，血液内科あるいは悪性リンパ腫，ATL の治療に精通した皮膚科医のもとで行うべき治療だが、それが諸事情により不可能な環境で、できる限りの治療を行う必要がある場合には、治療開始時及び経過中適時に適切な血液内科医の指導を受けたうえで、皮膚科医により行うものと考える。

2.4.3. 他院へ紹介する場合

皮膚病変を有する ATL 患者またはその疑いのある患者を紹介する場合、基本的には、血液内科、皮膚科の両診療科を標榜している医療機関へ紹介するのが適切である。これらの医療機関であっても、入院して専門的治療が行えない非常勤体制であるケース、また常勤体制でも地域によっては ATL を日常ほとんど診ることがないケースもある。患者紹介の経験もなく、どこに紹介すればよいかわからない場合では、「厚生労働省の HTLV-1 に関する情報」（http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou29/index.html）、「HTLV-1 情報サービス」の「医療機関検索」(http://www.htlv1joho.org/index_search.html)、国立がん研究センターの「がん情報サービス」の「病院を探す」（http://hospdb.ganjoho.jp/kyoten/）などの情報を用いて、地理的状況や患者のニーズも参考に適切な紹介先を決定する、あるいはがん診療連携拠点病院へ紹介するなどの方法が考えられる。がん診療連携拠点病院が必ずしも ATL の診療体制を整えているとは限らないが、「相談支援室」経由でそこから最も適切な医療機関への紹介を行うことは可能と考えられる。

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2014 年 2 月

Ⅲ. 研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
Tsukasaki K, Tobinai K.	HTLV-1-Assorted T-cell Diseases. 2013.	Francine Foss	T-cell Lymphomas	©Spring Science + Business Media	New York	2013	113-35
塚崎邦弘	成人Ｔ細胞白血病・リンパ腫.	山口徹 北原光夫 福井次矢	私はこう治療している・今日の治療指針 2013.	㈱医学書院	東京	2013	610-2
塚崎邦弘	成人Ｔ細胞白血病リンパ腫(ＡＴＬ)	一般社団法人日本血液学会	造血器腫瘍診療ガイドライン 2013 年度版	金原出版㈱	東京	2013.	228-38

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Tsukasaki K, Imaizumi Y, Tokura Y, Ohshima K, Kawai K, Utsunomiya A, et al.	Meeting report on the possible proposal of an extranodal primary cutaneous variant in the lymphoma type of adult T-cell leukemia-lymphoma.	J Dermatol	41	26-8	2014
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Ⅳ. 研究成果の刊行物・別刷

HTLV-1-Associated T-cell Diseases

8

Kunihiro Tsukasaki and Kensei Tobinai

Introduction

Adult T-cell leukemia-lymphoma (ATL) was first described in 1977 by Uchiyama and Takatsuki as a distinct clinico-pathological entity with a suspected viral etiology because of the clustering of the disease in the southwest region of Japan [1]. Subsequently, a novel RNA retrovirus, human T-cell leukemia/lymphotropic virus type I (HTLV-1), was isolated from a cell line established from leukemic cells of an ATL patient, and the finding of a clear association with ATL led to its inclusion among human carcinogenic pathogens [2–5]. In the mid-1980s and 1990s, several inflammatory diseases were reported to be associated with HTLV-1 [6–10]. At the same time, endemic areas for the virus and diseases have been found [reviewed in 11–13]. Diversity in ATL has been recognized and the subtype classification of the disease was proposed [14]. This chapter will characterize HTLV-1 and review the current recognition of ATL focusing on treatment of the disease.

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HTLV-1 Structure and Biology

HTLV-1 is a C-type oncovirus in the RNA retrovirus family [12, 13, 15]. Its genome of approximately 9 kb encodes three structural proteins, group angigen (gag), reverse transcriptase (pol), and envelop (env), the genes for which are flanked by 5′ and 3′ long terminal repeats (LTRs). In the 3′portion of the genome is a pX region that encodes the Tax, Rex, p21, p12, p13, and p30 proteins in its various reading frames [16, 17] (Fig. 8.1). Both Rex, a post-transcriptional regulator of viral expression, and Tax, a viral transcription factor co-operate with other viral products and cellular proteins to mediate viral replication [18, 19]. Antisense transcripts of the HTLV-1 provirus were reported. The transcripts can encode a novel basic leucine zipper protein, named HBZ, which interacts with several host genes and suppresses the activity of Tax [20–22]. Various isoforms of HBZ were reported to be steadily expressed in HTLV-1-infected cells and ATL cells in contrast to other viral genes, suggesting an important role in the development of ATL.

Methods of Detecting HTLV-1

Serological, virological, and molecular examinations can detect an HTLV-1 infection. As with other human retroviruses, HTLV-1 causes a persistent life-long infection after it synthesizes

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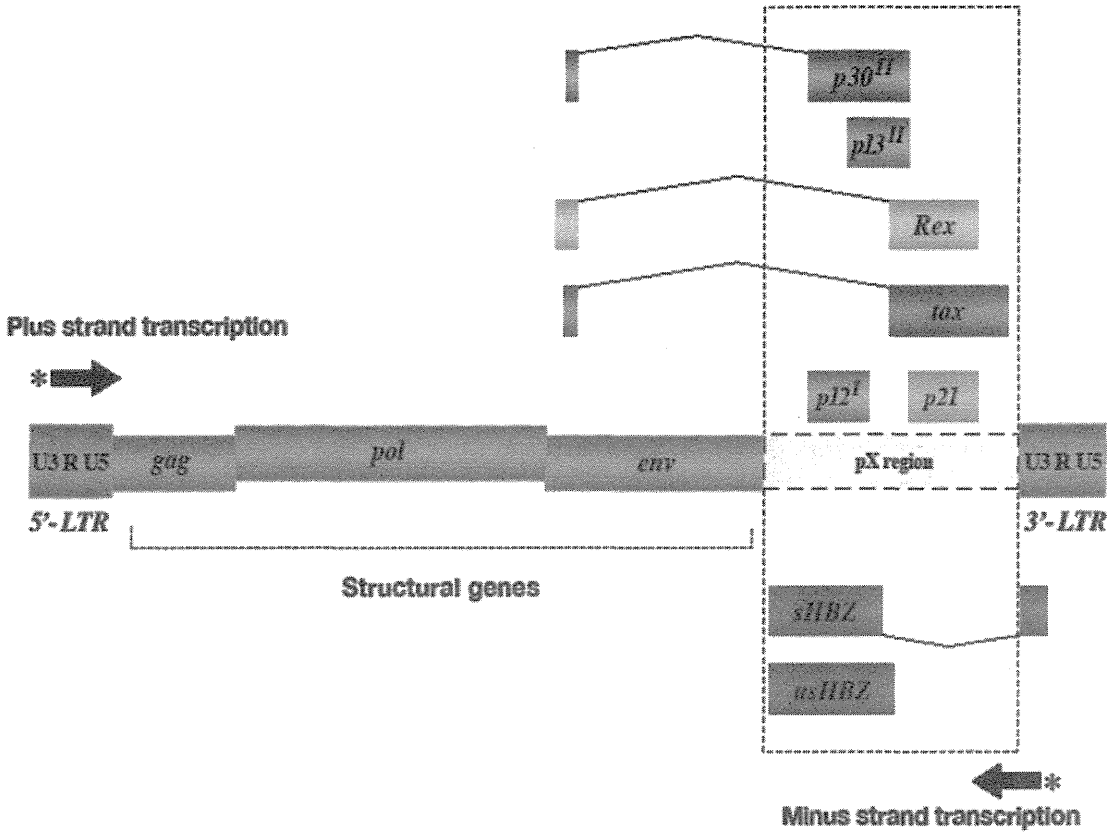

Fig. 8.1 Structure of HTLV-1. HTLV-1 encodes accessory and regulatory genes in the pXregion as well as viral structure genes. [Based on data from Satou Y, Matsuoka M. HTLV-1 and the host immune system: how the virus disrupts immune regulation, leading to HTLV-1-associated diseases. J Clin Exp Hematop. 2010; 50(1):1–8.]

copies of DNA by reverse transcriptase and integrates into the host's genome as a provirus.

Specific antibodies against HTLV-1 can be detected by enzyme-linked immunosorbent assay (ELISA), particle aggregation (PA), immunofluorescence microscopy, Western blotting (WB), or radioimmunoprecipitation. ELISA and PA are frequently used as screening assays [23–26]. To distinguish HTLV-1 from HTLV-2, which is less pathogenic, WB is usually necessary [27].

Fresh HTLV-1-infected cells from ATL patients or HTLV-1 carriers seldom express viral proteins except for HBZ [28, 29]. In contrast, in the presence of IL-2, short-term cultured HTLV-1-infected cells or established long-term T-cell lines usually produce viral particles and viral proteins, as demonstrated by electron microscopy and immunolabeling using antibodies to HTLV-1, respectively.

The clonal integration of HTLV-1 proviral DNA into infected T-cells can be demonstrated by Southern blot, inverse polymerase chain reaction (PCR), and/or ligation PCR assays [30–33]. Several investigators have analyzed the implications of the integration pattern of HTLV-I provirus in the progression of ATL [34, 35]. Neoplastic cells of ATL patients have only one complete copy of the HTLV-I provirus per cell in some cases (complete-type), but multiple complete copies in others (multiple-type). The HTLV-I proviruses in the remaining patients have a defective genome (defective-type). The median survival times for patients were 7 months, 24 months, and 33 months for defective-type, complete-type, and multiple-type ATL, respectively ($P=0.006$). Among the 52 patients examined, the HTLV-I integration patterns changed at disease progression in four patients (8%). In three of these four, the rearrangements of the TCR-β gene changed concomitantly, suggesting the appearance of a new ATL clone. The researchers concluded that the frequent clonal change of ATL

reflects the emergence of multiple premalignant clones in viral leukemogenesis. Tamiya and coworkers reported the presence of two types of defective virus. Among them, the type 2 defective virus with a deletion that includes the 5′ LTR was found more frequently in the acute and lymphoma types (39%, 21 of 54) than in the chronic type (6%, 1 of 18). It is postulated that the high frequency of the type 2 virus is caused by the genetic instability of the HTLV-I provirus and that the defective virus is selected because it escapes from the immune surveillance system in the host. Southern blotting and inverse PCR assays have sensitivity to detect the clonal disease, being able to identify the virus in a population with at least 5% and 1% of cells infected, respectively [33]. Also, about 20% of patients with HTLV-1-associated myelopathy (HAM)/tropical spastic paraparesis (TSP) and a small proportion of healthy HTLV-1 carriers have monoclonal HTLV-1 integration which can be detected by Southern blotting and/or inverse PCR [36, 37].

Epidemiology of HTLV-1

The three major routes of HTLV-1 transmission are mother-to-child infections via breast milk, sexual intercourses, and blood transfusions. Otherwise, HTLV-1 is not easily transmittable, since cell-to-cell contact is presumably required. Vertical transmission from mother to child is caused by breast-feeding beyond 4 to 6 months of age, after which time the protective IgG maternal antibodies decline [38]. HTLV-1-infected mononuclear cells are present in breast milk [39]. The overall rate of infection among breast-fed children from carrier mothers has been estimated at 10–30% [40]. Sexual transmission of HTLV-1 more frequently occurs from men to women than women to men. Infection by transfusion of contaminated cellular blood products is presumably the most efficient mode of transmission [41]. In contrast, fresh frozen plasma, which is acellular, is not infectious [42]. The transmission of HTLV-1 between intravenous drug abusers has been reported [43].

The Southwestern district of Japan has the highest prevalence of HTLV-1 infection in the world, but this infection is also endemic in the Caribbean basin, parts of Africa, Latin America, the Middle East, and the Pacific region [41, 44–48]. Many of the HTLV-1 carriers and ATL patients in the USA and Europe are immigrants from the above described endemic areas [49].

The seroprevalence of HTLV-1 in endemic areas is low and stable among children, but increases gradually with age, especially in women over 50 year of age [50]. In a cohort study in an endemic region of Japan, the seroprevalence of HTLV-1 in individuals between 16 and 39 years of age was 10% in both sexes; in contrast, the prevalence sky-rocketed to 30% in men and 50% in women over the age of 70 [51]. For several decades, the prevalence of HTLV-1 has declined drastically in endemic areas in Japan, probably because of birth cohort effects [52]. The elimination of HTLV-1 in endemic areas is now considered possible due to the natural decrease in the prevalence as well as intervention of transmission through blood transfusion and breast feeding.

HTLV-1-Related Diseases

HTLV-1 is associated with the development of ATL [1–5, 11–13], as well as HAM/TSP, a progressive form of chronic spastic myelopathy with demyelination of the spinal cord motor neurons, and HTLV-1-associated uveitis (HAU), a subacute inflammatory condition in which vitreous opacities are associated with mild iritis and mild retinal vasculitis [6, 7, 9]. Staphylococcal and streptococcal skin infections are common in the infective dermatitis (ID) syndrome described in Jamaica in association with HTLV-I infections in childhood [8]. Those individuals with ID were reported to be susceptible to ATL and HAM/TSP. ID was reported first in Jamaica and subsequently in Brazil and other countries of South America but rarely in Japan. In contrast, HAU was first reported in Japan and rarely occur in other countries. Other conditions reportedly associated with HTLV-1 include Sjogren's syndrome, polymyositis, alveolitis, arthritis, thyroiditis, and immune suppression [53–56].

Adult T-Cell Leukemia-Lymphoma

ATL is a distinct peripheral T-lymphocytic malignancy associated with a retrovirus designated human T-cell leukemia virus type I or human T-cell lymphotropic virus type I (HTLV-1) [1, 11–13, 57, 58]. Major prognostic indicators for ATL, which have been elucidated in 854 patients with ATL in Japan by the Lymphoma Study Group (LSG) of the Japan Clinical Oncology Group (JCOG) using multivariate analysis, were advanced performance status (PS), high lactic dehydrogenase (LDH) level, age of 40 years or more, more than three involved lesions, and hypercalcemia [56]. Also, a subclassification was proposed based on prognostic factors and clinical features of the disease (Table 8.1) [14]. The leukemic subtypes include all of the acute and chronic types and most of the smoldering type. The acute type has a rapid course with leukemic manifestation (>=2% ATL cells) with or without lymphocytosis ($>4\times10^9$/L) including ATL cells and most of the characteristic features of ATL-generalized lymphadenopathy, hepatosplenomegaly, skin involvement, other organ infiltration as shown in Figure 8.2, a high LDH value, and hypercalcemia. The symptoms and signs include abdominal pain, diarrhea, ascites, jaundice, unconsciousness, dyspnea, pleural effusion, cough, sputum, and chest X-ray abnormalities because of organ involvement, hypercalcemia, and/or opportunistic infections. The smoldering type shows an indolent course and 5% or more of leukemic cells in the peripheral blood without lymphocytosis, but may also include skin/lung involvement. The calcium level is less than the upper limit and LDH level is less than 1.5 times the upper limit in smoldering ATL. The chronic type, with absolute lymphocytosis (4×10^9/L) less frequently showing flower cell morphology than the acute type, is occasionally associated with skin involvement and lymphadenopathy and also

Table 8.1 Diagnostic Criteria for Clinical Subtypes of HTLV-1-associated ATL

	Smoldering	Chronic	Lymphoma	Acute
Anti-HTLV-I antibody	+	+	+	+
Lymphocyte (×103/μL)	<4	>=4‡	<4	*
Abnormal T lymphocytes	>=5%¶	+§	=<1%	+???
Flower cells with T-cell marker	†	†	No	+
LDH	=<1.5N	=<2N	*	*
Corrected Ca2+ (mEq/L)	<5.5	<5.5	*	*
Histology-proven lymphadenopathy	No	*	+	*
Tumor lesion A	*	*	*	*
Skin and/or lung	*	*	*	*
Lymph node	No	*		*
Liver	No	*	*	*
Spleen	No	*	*	*
Central nervous system	No	*	*	*
Bone	No	No	*	*
Ascites	No	No	*	*
Pleural effusion	No	No	*	*
Gastrointestinal tract	No	No	*	*

HTLV-I, human T-lymphotropic virus type I; LDH, lactate dehydrogenase; N normal upper limit
*No essential qualification except terms required for other subtype(s)
†Typical "flower cells" may be seen occasionally
‡Accompanied by T lymphocytosis (3.5 × 103/μL or more)
§If abnormal T lymphocytes are less than 5% in peripheral blood, histologically proven tumor lesion is required
Histologically proven skin and/or pulmonary lesion(s) is required if there are fewer than 5% abnormal T lymphocytes in peripheral blood
[Based on data from Shimoyama M, Members of the Lymphoma Study Group (1984–1987): Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. Br J Haematol 1991;79:428.]

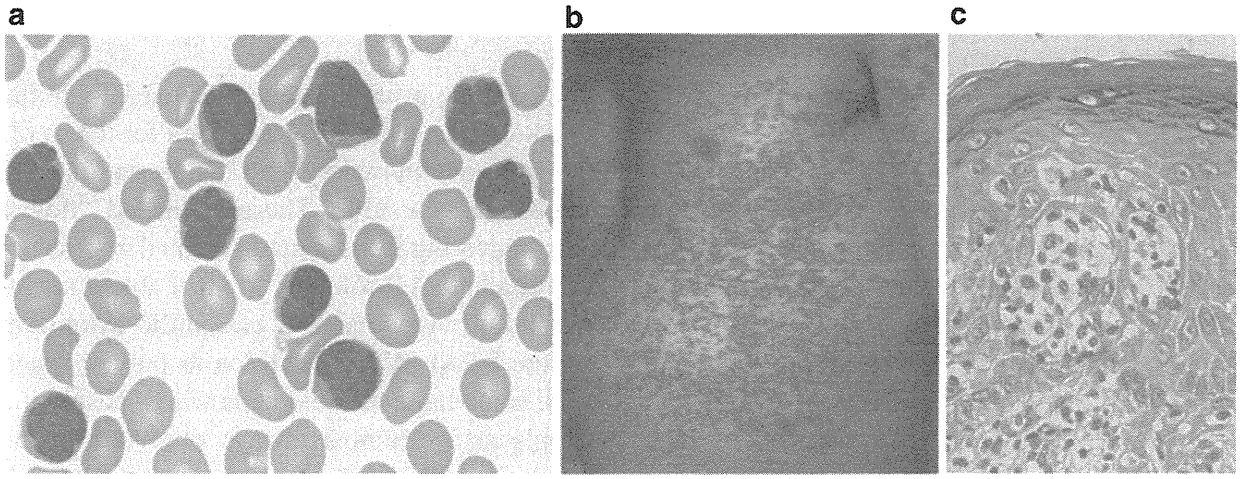

Fig. 8.2 (**a**) Leukemic cells (the so-called flower cells) showing characteristic polymorphic nuclei with condensed chromatin and agulanular and basophilic cytoplasm. (**b**) Photograph of skin lesion in a patient with acute-type ATL. (**c**) Histology of skin infiltration of ATL cells in the same patient; infiltrating ATL cells are present in the epidermis forming a Pautrer's micro-abscess.

usually shows a relatively indolent course. The calcium level is less than the upper limit and the LDH level is less than double the upper limit of the chronic type. The lymphoma type presents with the manifestations of a lymphoma without leukemic cells, frequently with high LDH/Ca levels, a rapid course, and symptoms and signs similar to the acute type. In case of ATL, clinical subtype is more important than Ann Arbor stage for predicting prognosis and deciding treatment.

Additional factors associated with a poor prognosis include thrombocytopenia, eosinophilia, bone marrow involvement, a high interleukin (IL)-5 serum-level, CC chemokine receptor 4 (CCR4) expression, lung resistance-related protein, p53 mutation, and p16 deletion by multivariate analysis [59–65]. Specific for the chronic type of ATL, high LDH, high blood urea nitrogen (BUN), and low albumin levels were identified as factors for a poor prognosis by multivariate analysis [11]. Primary cutaneous tumoral type, although generally included among smoldering ATL, had a poor prognosis in one uni-variate analysis [66].

Epidemiology of ATL

The average age at onset of ATL in Japan is 57 years, which is about 15 years older than in the Caribbean, South America, and Africa [67–69]. This may reflect unknown environmental or ethnic cofactors in the multi-step leukemogenesis of this disease. The estimated annual incidence in Japan is about 1 per 1,000 HTLV-1 carriers over 40 years of age, with males affected about twice as often [70]. The cumulative life time risk for ATL among HTLV-1 carriers has been estimated at 1–5% in both sexes in Japan and in Jamaica [71, 72]. HTLV-1 infection early in life, presumably from breast feeding, is crucial in the development of ATL; 100% of mothers of ATL patients examined were HTLV-1 carriers as compared to about 30% of mothers of HAM/TSP patients [73]. HTLV-1infection by blood transfusion is associated with a higher risk for the development of HAM/TSP than infection by other routes [74]. In contrast, very few cases of ATL after HTLV-1 infection by blood transfusion have been reported [75, 76]. Interestingly, those affected had blood transfusions for a preceding hematological malignancy, and developed ATL within 11 years after HTLV-1infection. Factors reportedly associated with the onset of ATL include: HTLV-1 infection early in life, increase in age, male sex, family history of ATL, past history of infective dermatitis, smoking of tobacco, serum titers of antibody against HTLV-1, and several HLA subtypes [77–82].

Recently, HTLV-1 proviral loads have been proposed as an important predictor of ATL, but only a few small prospective studies have been

conducted. Recently, Iwanaga and colleagues evaluated 1,218 asymptomatic HTLV-1 carriers (426 males and 792 females) who were enrolled during 2002–2008 for a prospective study on the development of ATL [83]. The proviral load at enrollment was significantly higher in males than females (median, 2.10 vs. 1.39 copies/100 peripheral blood mononuclear cells (PBMC; $P<0.0001$)), in those aged 40 or more years and in those with a family history of ATL. During the follow-up period, 14 participants developed acute ATL. Their baseline proviral loads were high (range, 4.17–28.58 copies/100 PBMC). Multivariate Cox regression analyses indicated that not only a higher proviral load but also advanced age, a family history of ATL, and the first opportunity for HTLV-1 testing during treatment for other diseases were independent risk factors for the progression of ATL from a carrier status.

Clinical Features

ATL patients show a variety of clinical manifestations because of various complications of organ involvement by ATL cells, opportunistic infections, and/or hypercalcemia [11–14]. These three often contribute to the extremely high mortality of the disease. Lymph node, liver, spleen, and skin lesions are frequently observed. Although less frequent, the digestive tract, the lungs, the central nervous system, bone, and/or other organs may be involved. Large nodules, plaques, ulcers, and erythroderma are common skin lesions [66, 84]. Immune suppression is common. Approximately 26% of 854 patients with ATL had active infections at diagnosis in a prior nationwide study in Japan [14]. The incidence was highest in the chronic and smoldering types (36%) and lower in the acute (27%) and lymphoma types (11%). The infections were bacterial in 43%, fungal in 31%, protozoal in 18%, and viral in 8% of patients. The immunodeficiency at presentation in ATL patients can be exacerbated by cytotoxic chemotherapy. Individuals with indolent ATL might have no manifestation of the disease and are identified only by health check-ups and laboratory examinations.

Laboratory Findings

ATL cells are usually detected quite easily in the blood of affected individuals except for the smoldering type with mainly skin manifestations and lymphoma type [14]. These so called "flower cells" have highly indented or lobulated nuclei with condensed chromatin, small or absent nucleoli, and an agranular and basophilic cytoplasm (Figure 8.2A) [85]. In addition to polylobulated cells, some large blastoid cells with a basophilic cytoplasm are almost always observed in the blood film. Furthermore, the diversity of cell morphology in ATL is associated with prognostic factors, an aberrant immmunophenotype, and a defective HTLV-1 genotype [86]. Five percent or more abnormal T-lymphocytes in peripheral blood confirmed by cytology and immunophenotyping are required to diagnose ATL in cases without histologically proven tumor lesions [14].

The histological analysis of aberrant cutaneous lesions or lymph nodes is essential for the diagnosis of the smoldering type with mainly skin manifestations and lymphoma type of ATL, respectively. Because ATL cells in the skin and lymph node can vary in size from small to large and in form from pleomorphic to anaplastic and Hodgkin-like cell with no specific histological pattern of involvement, differentiating between Sezary syndrome, other peripheral T-cell lymphomas (PTCLs), and Hodgkin lymphoma versus ATL can at times be difficult without examinations for HTLV-1 serotype/genotype [13, 87].

The white blood cell count ranges from normal to 500×10^9/L. Marked leukocytosis of >30 and lymphocytes of 15× have been observed in about 40% of acute ATLs and 25% of chronic ATLs, but not in the other two subtypes (lymphoma, smoldering) [14]. Granulocytosis of more than 8× is frequently observed (about 40% of acute type and 15% of the other three types) even in the absence of infection. Eosinophilia is frequent (21%) as compared to other T- or B-lymphomas. Neutrophilia and eosinophilia are presumably related to the release of cytokines {chiefly granulocyte-macrophage colony-stimulating factor (GM-CSF) and Interleukin (IL)-5}

by malignant cells. Anemia and thrombocytopenia are less frequently observed, probably because much of the bone marrow is spared by the leukemia. Some of the hematological abnormalities were associated with the prognosis of ATL as described previously.

Hypercalcemia is the most distinctive laboratory abnormality in ATL as compared to other lymphoid malignancies and is observed in 31% of patients (50% in acute type, 17% in lymphoma type, and 0% in the other two types) at onset [14]. Individuals with hypercalcemia do not usually have osteolytic bone lesions. Parathyroid hormone-related protein or receptor activator of nuclear factor kappa B ligand produced by ATL cells is considered the main factor causing hypercalcemia [88, 89].

Similar to serum LDH, β2-microglobulin, and serum thymidine kinase levels reflecting disease bulk/activity, the level of the soluble form of interleukin (IL)-2 receptor alpha-chain is elevated in the order acute/lymphoma-type ATL, smoldering chronic-type ATL, and HTLV-1 carriers as compared with normal individuals, perhaps with better accuracy than the other markers [90–92]. These serum markers are useful for detecting the acute transformation of indolent ATL as well as the early relapse of ATL after achieving responses by therapy.

Prototypical ATL cells have a mature alpha–beta T-cell phenotype, that is, they are terminal deoxynucleotidyl transferase (TdT)-negative, CDla-negative, T-cell receptor alpha–beta-positive, CD2-positive and CD5, CD45RO and CD29-positive, and frequently do not express CD7 and CD26. A decline in the CD3 level with the appearance of CD25 indicates that the ATL cells are in an activated state. Most ATL cells are CD52-positive, but some are negative and this may correlate with the co-expression of CD30. About 90% of cases are CD4-positive and CD8-negative, and in rare cases either co-express CD4 and CD8, are negative for both markers, or are only CD8-positive [93]. CCR4 is expressed in more than 90% of cases and associated with a poor prognosis. Recent studies have suggested that the cells of some ATL may be the equivalent of regulatory T-cells because of the high frequency of expression of CD25/CCR4 and about half of FoxP3 [62, 94].

Chromosomal abnormalities detected by cytogenetics or comparative genomic hybridization are often more complex and more frequent in aggressive ATL than in indolent ATL, with aneuploidy and several hot spots such as 14q and 3p [95, 96]. A more sensitive array-CGH revealed that the lymphoma type had significantly more frequent gains at 1q, 2p, 4q, 7p, and 7q, and losses at 10p, 13q, 16q, and 18p, whereas the acute type showed a gain at 3/3p, but no specific pattern of abnormality has been identified which is in contrast to Burkitt leukemia/lymphoma with a *myc* gene rearrangement induced by Epstein–Barr virus [97, 98].

DNA microarray analyses of the transcriptomes of ATL cells at the chronic and acute stages to elucidate the mechanism of stage progression in this disease revealed that several hundred genes were modulated in expression including those for MET, a receptor tyrosine kinase for hepatocyte growth factor, and cell adhesion molecule, TSLC1 [99, 100].

Diagnosis of ATL

The diagnosis of typical ATL is not difficult and is based on clinical features, ATL cell morphology, mature helper-T-cell phenotype, and ant-HTLV-1 antibody in most cases [13, 55]. Those rare cases which might be difficult to diagnose can be shown to have the monoclonal integration of HTLV-1 proviral DNA in the malignant cells as determined by Southern blotting. However, the monoclonal integration of HTLV-1 is also detected in some HAM/TSP patients and HTLV-1 carriers [36, 37]. After the diagnosis of ATL, subclassification of the disease is necessary for the selection of appropriate treatment [14, 57].

Clinical Course and Treatment of ATL

Treatment decisions should be based on the ATL subclassification and the prognostic factors at onset including those related with ATL and co-morbidity [57]. As mentioned above,

subclassification of this disease has been proposed based on the prognosis and clinical manifestations. Without treatment, most patients with acute-/lymphoma/type ATL die of the disease or infections within weeks or months. More than half of patients with smoldering ATL survive for more than 5 years without chemotherapy and transformation to aggressive ATL. Chronic ATL has the most diverse prognosis among the subtypes and could be divided into favorable and unfavorable by clinical parameters (serum albumin, BUN, and LDH levels) after a multivariate analysis [11].

Current treatment options for ATL include watchful waiting until disease progression, interferon alpha (IFN) and zidobudine (AZT) therapy, multi-agent chemotherapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT), and a new agent [57].

Watchful Waiting

At present, no standard treatment for ATL exists. Therefore, patients with the smoldering or favorable chronic type, who may survive one or more years without chemotherapy, excluding topical therapy for cutaneous lesions, should be observed and therapy should be delayed until progression of the disease [57]. However, it was recently found that the long-term prognosis of such patients was poorer than expected. In a long-term follow-up study for 78 patients with indolent ATL (favorable chronic- or smoldering-type) with a policy of watchful waiting until disease progression at a single institution, the median survival time was 5.3 years with no plateau in the survival curve. Twelve patients remained alive for >10 years, 32 progressed to acute ATL, and 51 died [101]. These findings suggest that even "indolent" ATL patients should be carefully observed in clinical practice. Further study is required to establish appropriate management practices for indolent ATL.

Chemotherapy

Since 1978, chemotherapy trials have been consecutively conducted for patients newly diagnosed with ATL by JCOG's LSG (Table 8.2) [102–107]. Between 1981 and 1983, JCOG conducted a phase III trial (JCOG8101) to evaluate LSG1-VEPA (vincristine, cyclophosphamide, prednisone, and doxorubicin) vs. LSG2-VEPA-M (VEPA plus methotrexate (MTX)) for advanced non-Hodgkin lymphoma (NHL), including ATL [102, 103]. The complete response (CR) rate of LSG2-VEPA-M for ATL (37%) was higher than that of LSG1-VEPA (17%; $P=0.09$). However, the CR rate was significantly lower for ATL than for B-cell NHL and PTCL other than ATL ($P<0.001$). The median survival time of the 54 patients with ATL was 6 months, and the estimated 4-year survival rate was 8%.

In 1987, JCOG initiated a multicenter phase II study (JCOG8701) of a multi-agent combination chemotherapy (LSG4) for advanced aggressive NHL (including ATL). LSG4 consisted of three regimens: (1) VEPA-B (VEPA plus bleomycin),

Table 8.2 Results of sequential chemotherapeutic trials of untreated patients with ATL (JCOG-LSG)

	J7801	J8101	J8701	J9109		J9303	JCOG9801
	LSG1	LSG1/LSG2	LSG4	LSG11		LSG15	mLSG15/mLSG19
Pts. No.	18	54	43	62	96	57	61
CR (%)	16.7	27.8	41.9	28.3	35.5	40.4	24.6
CR+PR (%)	51.6	80.6	72.0	65.6			
MST (months)	7.5	7.5	8.0	7.4	13.0	12.7	10.9
2-year survival (%)	17.0	31.3					
3-year survival (%)	10.0	21.9	23.6	12.7			
4-year survival (%)	8.0	11.6					

CR complete remission, PR partial remission, MST median survival time