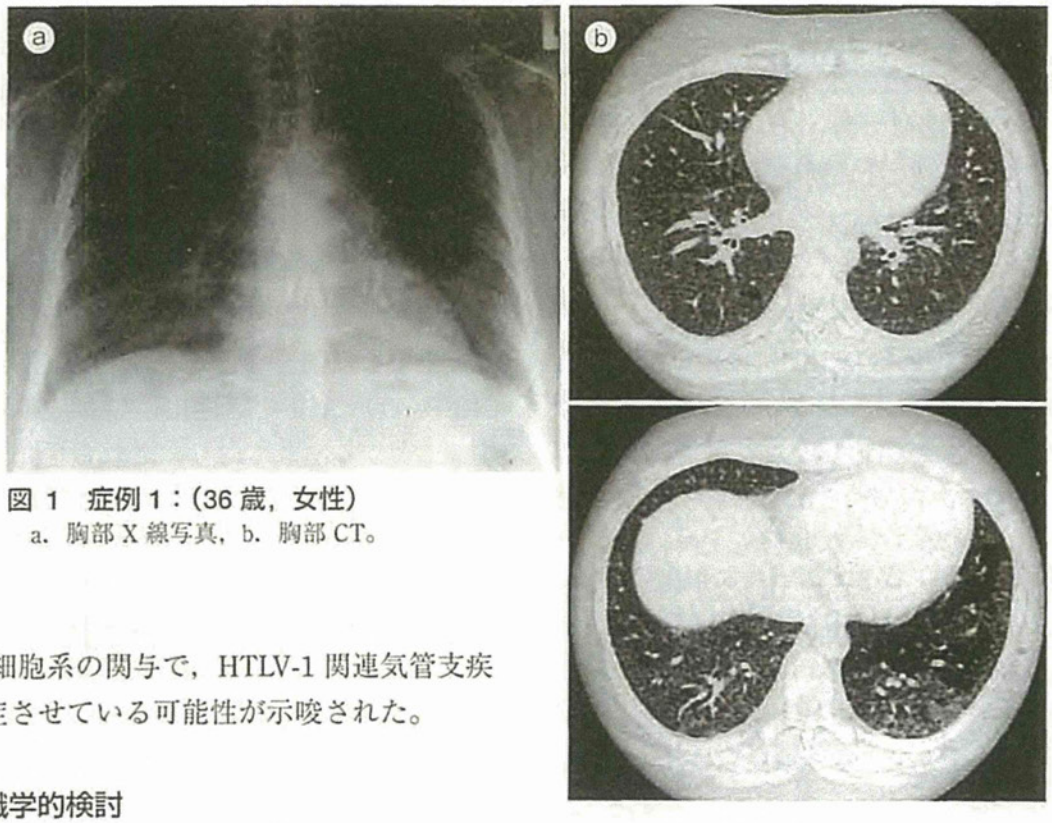

図 1　症例 1：(36 歳，女性)
a．胸部 X 線写真，b．胸部 CT。

特に Th1 細胞系の関与で，HTLV-1 関連気管支疾病変を発症させている可能性が示唆された。

2）肺組織学的検討

HTLV-1 関連肺疾患症例の肺組織における組織学的検討の結果，肺上皮細胞と浸潤しているリンパ球に TAX の発現を確認している[11]。

3）BAL 施行症例における抗 HTLV-1 抗体陽性者の肺病変に関しての画像的検討

a．方法

当科における約 12 年間の BAL 施行症例のべ 467 例のうち，抗 HTLV-1 抗体を測定し得た 228 例での検討。

b．結果

①抗 HTLV-1 抗体を測定し得た肺病変のある BAL 症例 228 例のうち，74 例 32.5%が抗 HTLV-1 抗体陽性であった（本邦の抗 HTLV-1 抗体陽性率の報告は地域によって 0.3 から 30%と差があるが，32.5%は高値）。平均年齢 60.7 歳。男性：女性＝24：50 人（そのうち ATL 発症は男性：女性＝5：13 人，HTLV-1 キャリアで DPB 様所見は男性：女性＝3：13 人，HTLV-1 キャリアで IP 様所見は男性：女性＝6：1 人と性差あり）。

②HTLV-1 抗体陽性 74 例の BAL 施行時の肺野陰影の内訳：ATL 発症 18 例（ニューモシスチス肺炎 5 例，DPB 様陰影 2 例，多発斑状陰影 2 例，その他），HTLV-1 associated myelopathy/tropical spastic paraparesis（HAM/TSP）：2 例（ともに DPB 様陰影），HTLV-1 キャリア：54 例〔DPB 様陰影 16 例（30.0%），UIP 様陰影 3 例（5.6%），気管支拡張 3 例（5.6%），その他〕であった。DPB 様の気道病変がやはり多い結果であったが，UIP あるいは NSIP 様陰影など，DPB 様以外の陰影も少なくはなかった（表，図 2〜7）。

5 考　察

HTLV-1 関連肺病変（気道病変含む）に関しては，ATL 発症者，HTLV-1 キャリアとともに，詳細不明でいまだ混沌とした状態である。HTLV-1 キャリアにおいては，当科の検討でも，これまで報告されてきた DPB 様の気道病変がやはり多い結果であったが，UIP あるいは NSIP 様陰影など，DPB 様以外の陰影も少なくはない。DPB 様所見を合併した HTLV-1 キャリアからの ATL 発症率が高いとの報告があり（当科症例あり。図 3），HTLV-1 キャリアをフォローする際には常に ATL 発症に関しても留意することが大切である

表　HTLV-1 抗体 陽性 74 例の BAL 時の肺野陰影の内訳

ATL 発症：18 例
　カリニ肺炎（5 例），DPB 様陰影（2 例），多発斑状陰影（2 例），下葉粒状陰影（1 例），びまん性すりガラス陰影（1 例），肺門陰影増強（1 例），細菌性肺炎（1 例），右中葉腫瘤陰影（1 例），詳細不明（4 例）
HAM/TSP：2 例
　ともに DPB 様陰影
HTLV-1 キャリア：54 例
　小葉中心性粒状陰影，細気管支炎陰影（＝DPB 様）（16 例，30.0%），UIP 様陰影（3 例，5.6%）
　気管支拡張症様陰影（3 例，5.6%），NSIP 様陰影（2 例，3.7%），AIP 様陰影（1 例，1.9%），LIP 様陰影（1 例，1.9%）
　その他：
　　過敏性肺臓炎合併（1 例），慢性好酸球肺炎合併（1 例），器質化肺炎様陰影（1 例），他基礎疾患あり（8 例）
　　陰影分類難（6 例），陰影詳細不明（3 例），明らかな陰影なし（8 例）
　　（BAL の施行理由が慢性咳嗽や不明熱，胸水の原因精査など）

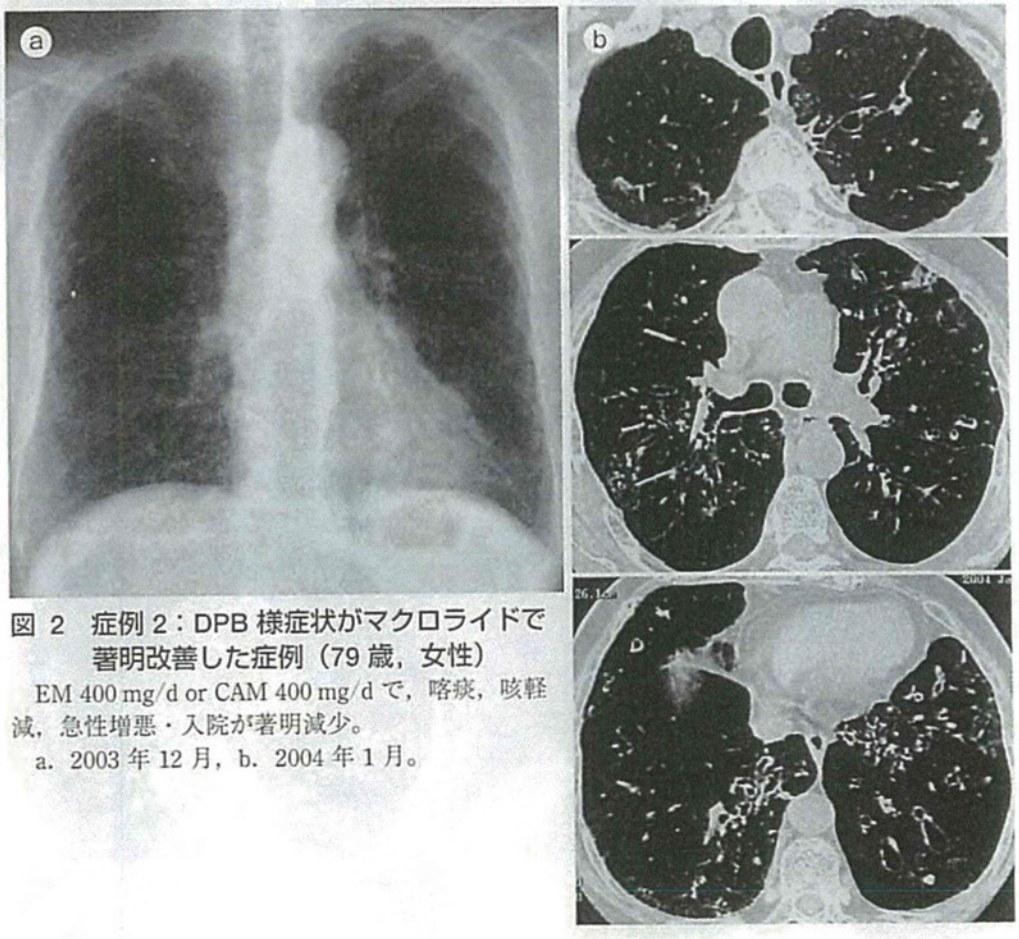

図 2　症例 2：DPB 様症状がマクロライドで著明改善した症例（79 歳，女性）
EM 400 mg/d or CAM 400 mg/d で，喀痰，咳軽減，急性増悪・入院が著明減少。
a. 2003 年 12 月，b. 2004 年 1 月。

と思われる。HTLV-1 関連気道病変および肺病変の発症病態解析に関しては，今後とも症例の蓄積が必須であり，サイトカインネットワーク，免疫系，および遺伝系などのさらなる詳細な検討が必要と思われる。そして症例の治療に結びついていくことが望まれる。

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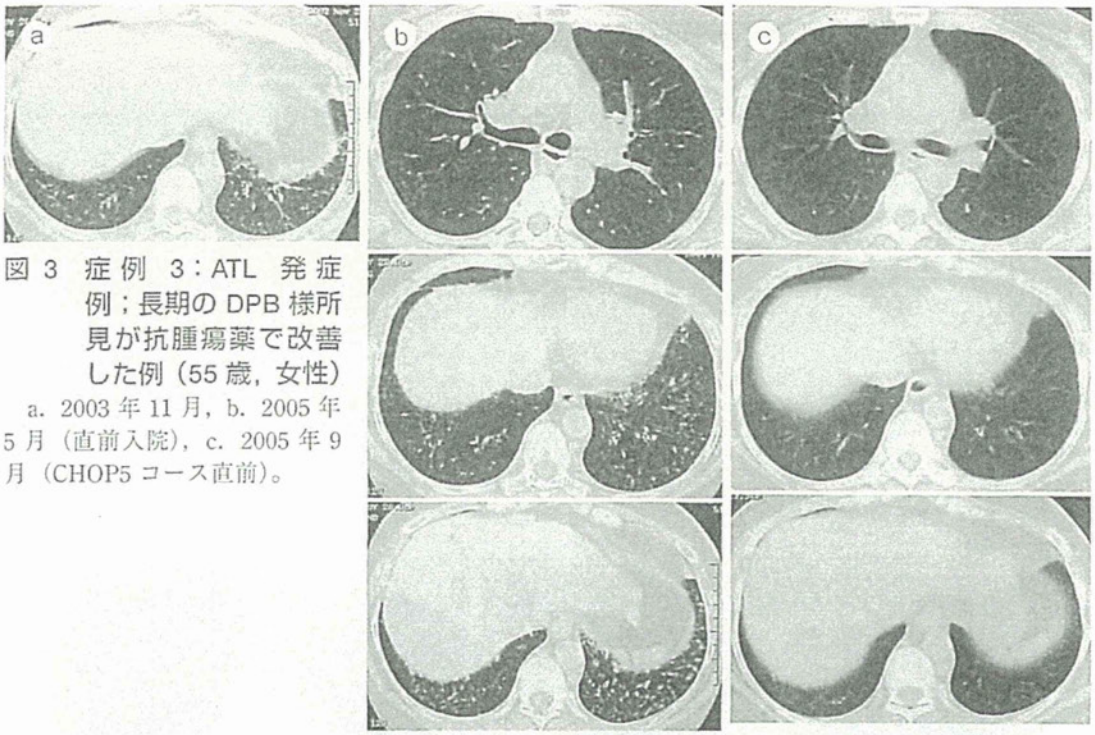

図 3　症例 3：ATL 発症例；長期の DPB 様所見が抗腫瘍薬で改善した例（55 歳，女性）

a. 2003 年 11 月，b. 2005 年 5 月（直前入院），c. 2005 年 9 月（CHOP5 コース直前）。

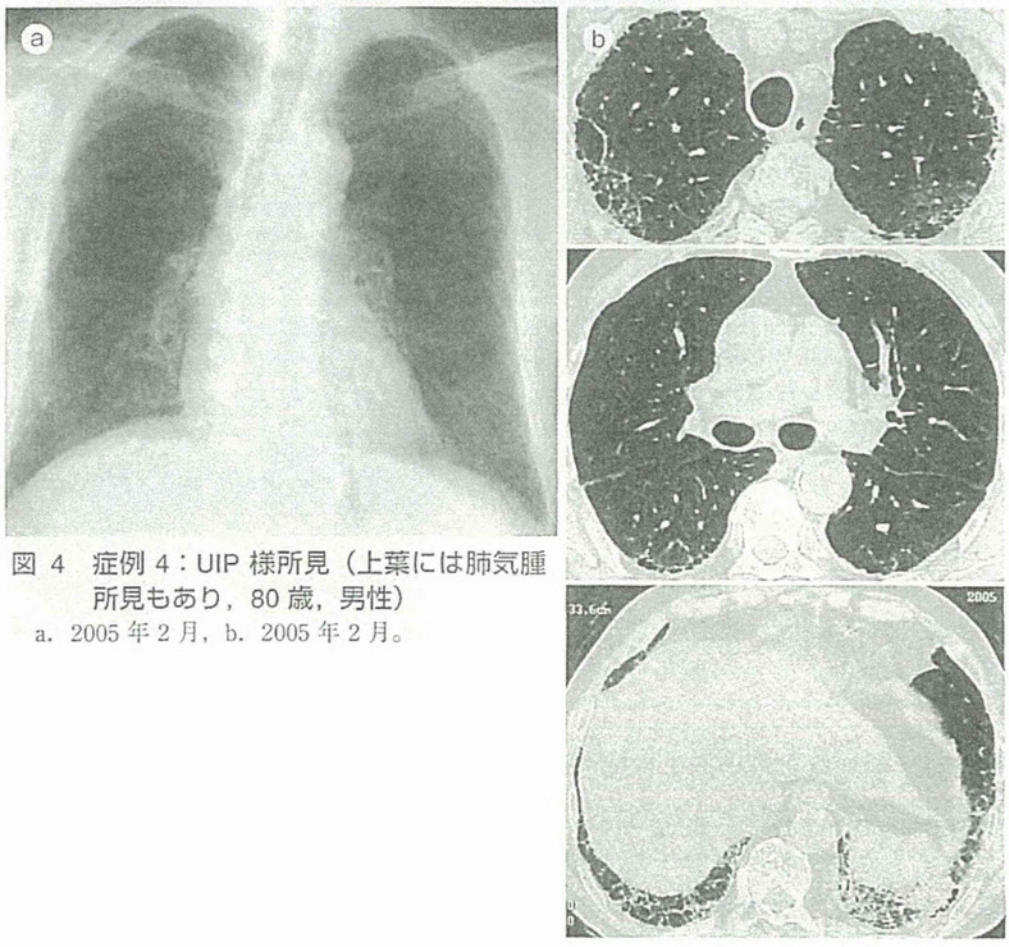

図 4　症例 4：UIP 様所見（上葉には肺気腫所見もあり，80 歳，男性）

a. 2005 年 2 月，b. 2005 年 2 月。

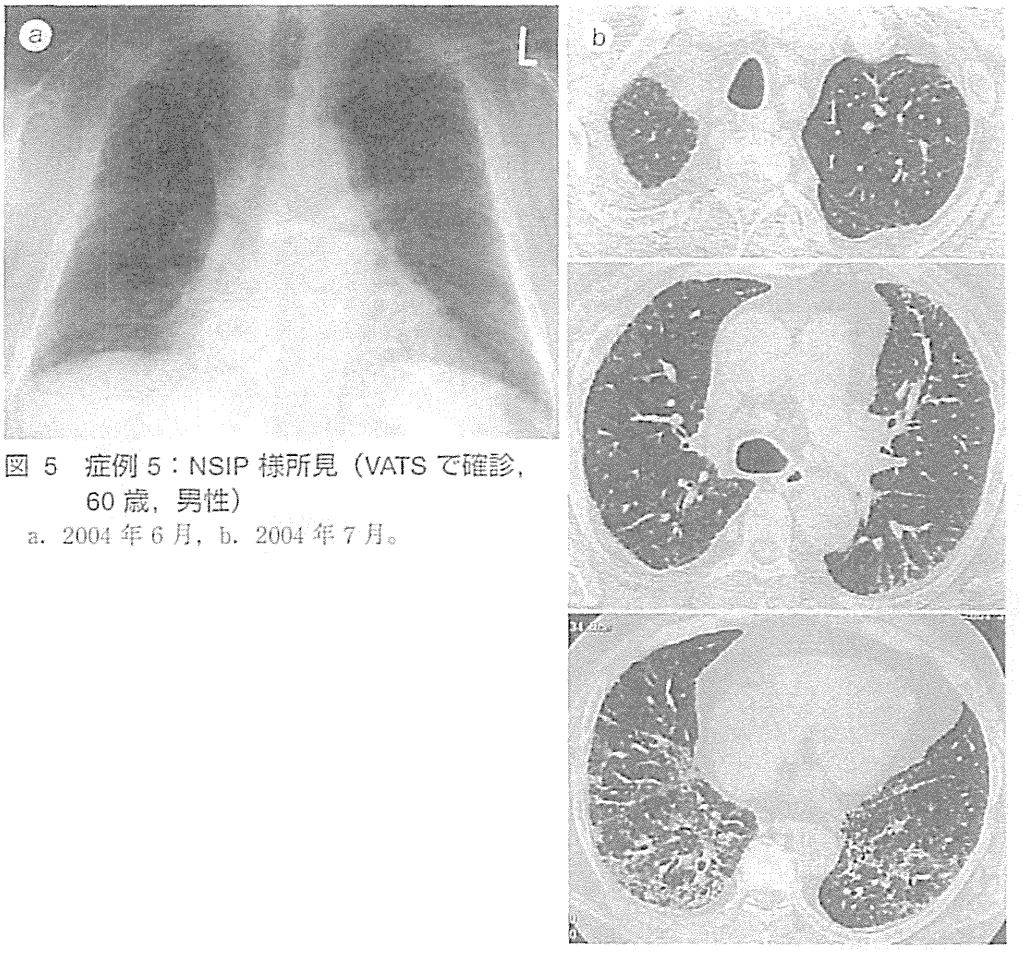

図 5　症例 5：NSIP 様所見（VATS で確診，60 歳，男性）
a．2004 年 6 月，b．2004 年 7 月。

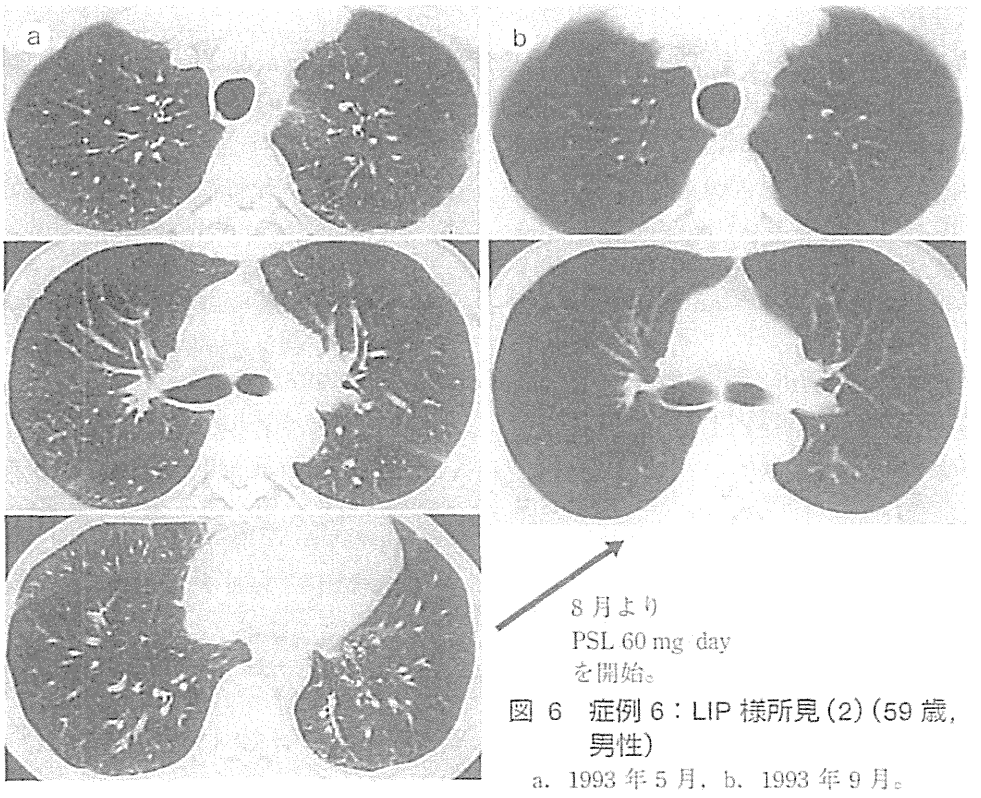

図 6　症例 6：LIP 様所見（2）（59 歳，男性）
a．1993 年 5 月，b．1993 年 9 月。

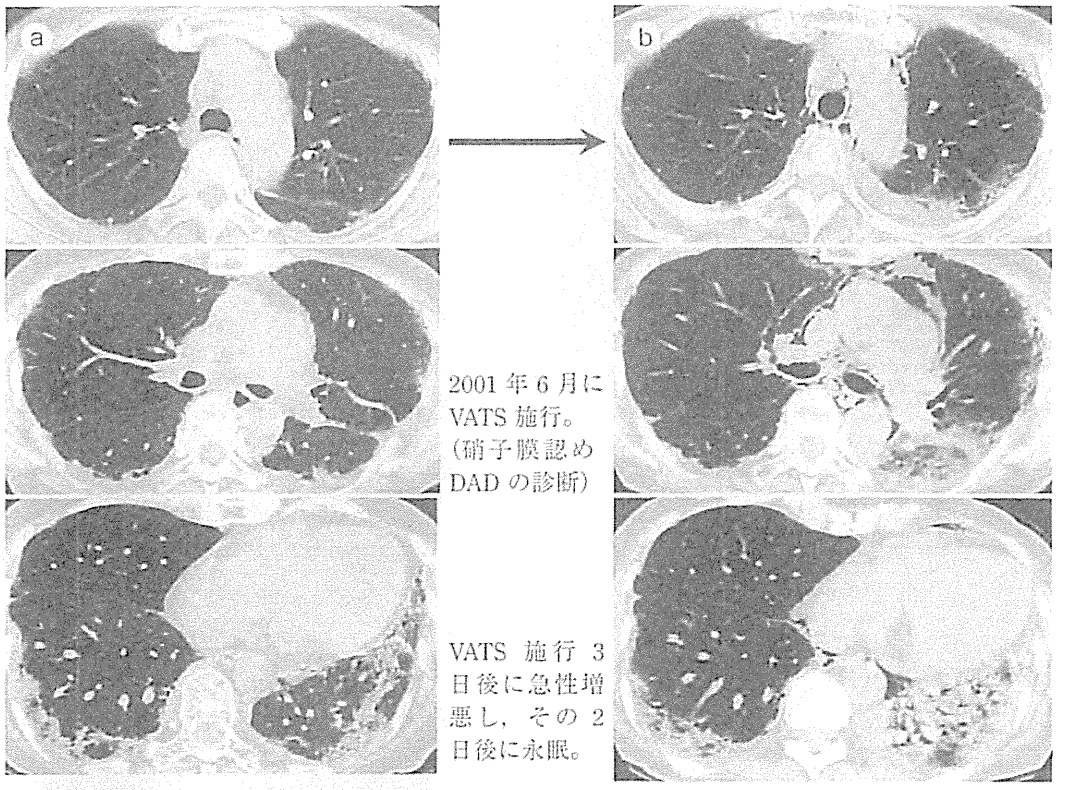

図 7　症例 7：AIP 所見（63 歳，女性）
a. 2001 年 6 月，b. a. の 15 日後。

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6. 糞線虫過剰感染症候群

Strongyloides stercoralis hyperinfection syndrome

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診断の要点	●沖縄・奄美地方出身者における下痢，低栄養患者をみた場合には本症を念頭に置く． ●腸管の機能障害を伴う肺炎患者では本症を念頭に置く． ●成人の化膿性髄膜炎をみた場合には本症を念頭に置く．
治療の要点	●ivermectin を虫体が陰性となるまで，繰り返し投与する． ●腸内細菌をターゲットとした抗菌薬を併用する．

歴史と定義

糞線虫は 1876 年にベトナムから帰還したフランス人兵士のあいだでみられた難治性下痢患者より発見された．本虫は熱帯・亜熱帯に広く分布し，わが国の浸淫地は沖縄・奄美地方である．他の地域での患者のほとんどはこれらの浸淫地の出身者である．また，同地方は，成人 T 細胞性白血病(adult T-cell leukemia：ATL)の原因であるヒト T 細胞白血病ウイルス 1 型(HTLV-1)の浸淫地でもあり，糞線虫との重複感染が問題となっている．HTLV-1 感染者における糞線虫感染率は陰性者の約 2 倍であり，重症例の約 8 割が HTLV-1 抗体陽性者，あるいは ATL 患者からの発症である[1]．

本虫の生活史であるが，感染型幼虫であるフィラリア(F)型幼虫は土壌より経皮感染後，血流を介し肺に達し，気管をさかのぼり嚥下され，最終的に十二指腸に達して成虫となる．そこで産卵し，孵化したラブジチス(R)型幼虫は便とともに体外に排出される．以上が通常の糞線虫の生活史であるが，本虫には自家感染という特殊な経路がある．これは，R 型幼虫が体外に排泄される前に F 型幼虫となり，腸管もしくは肛門周囲の皮膚より再感染するという経路である．この自家感染のため，感染者は長期にわたり糞線虫に感染した状態となる．ステロイド薬使用や HTLV-1 感染状態などにより宿主の免疫能が低下すると，この自家感染が激しく増強し過剰感染状態となる．過剰感染の状態では多数の幼虫が消化管のみならず，全身の臓器，組織に散布され，過剰感染症候群，播種性糞線虫症といわれる深刻な病態を呈する．

臨床の実際

1．症状・徴候

消化器症状は糞線虫症における一般的な症状であり，軽症例では軽度の腹痛，腹鳴，腹満感，軟便などの症状がときに認められる．過剰感染状態となると腸管の機能障害(麻痺性イレウス，吸収不良症候群，蛋白漏出性腸症)や消化管出血の合併が認められるようになる．また，十二指腸乳頭部の炎症により閉塞性黄疸，膵炎を呈する場合もある．自家感染時に肺に移行する幼虫数が増加すると，発熱，咳嗽，喘鳴，血痰などが出現し，喀痰内に幼虫が検出されるようになる．呼吸器症状の出現または喀痰から虫体が検出される場合は，過剰感染状態であり注意が必要である．糞線虫は自家感染の際に腸管より多量の腸内細菌をもち込むため，敗血症，細菌性肺炎，化膿性髄膜炎を引き起こすことがある．原因微生物としては大腸菌，肺炎桿菌，腸球菌が多い．

臨床検査値に関しては好酸球，IgE 値の上昇が認められる場合があるが，過剰感染時には上昇しない場合が多いため，注意が必要である．

画像所見に関しては，腹部 X 線にてイレウス像，十二指腸内視鏡では粘膜の浮腫，発赤，白色絨毛，管腔の狭窄などの所見を呈し，生検にて糞線虫の雌成虫を認める[2]．胸部 X 線にて肺炎像，

ARDS の所見を呈する場合もある．

診断は基本的には便から虫体(R 型幼虫)を証明することによる．重症例では喀痰，胃十二指腸液，腹水などからも検出されるようになる．検出方法としては普通寒天平板培地法がもっとも優れており，他法の数倍の感度がある[3]．その他，内視鏡下の生検で診断される場合もある．

2．治　　療

ivermectin を体重 1 kg 当たり 200 μg を投与する[4]．通常は糞線虫の自家感染を考慮して，治療は 2 週間隔 2 回投与を原則とする．しかし，過剰感染の場合には，糞線虫が陰性化するまで 1〜2 週間隔で 4 回以上投与する．また，人工呼吸器が必要となるなど危機的な状況においては 5〜7 日間連続投与を試みる．イレウスなどで経口不能の場合には，イレウス管などより粉砕して投与する．播種性糞線虫症においては，駆虫のみでは敗血症，肺炎，髄膜炎は治癒しないため，腸内細菌をターゲットにした抗菌薬を必ず併用する．

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2 成人T細胞白血病/リンパ腫

天野 正宏

ヒトT細胞白血病ウイルス1型（HTLV-1）によるT細胞の悪性新生物である．2008年のWHO分類（第4版）では，菌状息肉症（MF）やSézary症候群（SS）とともに，皮膚T細胞・NK細胞リンパ腫のなかに分類されている．母乳を介した感染が90%以上を占め，HTLV-1の感染後，約50～60年間という長い潜伏期間の後，1～5%が成人T細胞白血病/リンパ腫（adult T-cell leukemia/lymphoma：ATLL）を発症するとされる．HTLV-1の高度浸淫地域，すなわち日本南西部，カリブ海諸島，南アメリカ，中央アフリカの諸地域では，ATLLは一種の風土病とされてきた．わが国南西部では20数年前から抗HTLV-1抗体陽性の妊婦に対し母乳中止や制限措置が功を奏し，抗HTLV-1抗体陽性者が減少してきた．しかし最近，人口移動などにより抗HTLV-1抗体陽性者が全国的な広がりをみせているとの報告を受け，2010年，政府および厚生労働省が全国的に妊婦に全例抗HTLV-1抗体検査を義務付け，またATLLやHTLV-1関連脊髄症（HAM）を含めたHTLV-1関連疾患の治療および研究に予算をつけている．

ATLLは末梢血液像（特に異常リンパ球%），血清LDH（lactate dehydrogenase）値，血清補正カルシウム値，臓器病変の有無などを基に，急性型，リンパ腫型，慢性型，くすぶり型に分けられる．急性型やリンパ腫型ATLLは治療抵抗性を示し，極めて予後不良である．これに対し，慢性型やくすぶり型ATLLは慢性に経過するが，急性転化することもある．ATLLのなかには末梢血液に異常リンパ球もなく，またリンパ節浸潤や臓器病変を伴わず，皮膚病変（特異疹）だけを認めることもあり，急性型やリンパ腫型ATLLと同様に予後不良であり，皮膚型ATLLの存在が提唱されている．筆者らの皮膚型ATLLの診断基準（私案）は，確定診断時に，①ATLLの特異疹があり，②リンパ球数＜4,000/μL，③皮膚以外に臓器浸潤を認めない，である．

診断と検査

ATLLの診断では，まず患者がどの臨床病型にあるかが重要である．なぜなら病型によって予後が決定するからである．急性型やリンパ腫型ATLLの生存期間は2週間～1年未満である．慢性型やくすぶり型ATLLでは，より遷延性の臨床経過をとり長期間生存することもあるが，急性型ATLLへ転化することがあるので，注意深い経過観察が必要である．

診断には，まず採血にて抗HTLV-1抗体の有無をチェックし，陽性であれば末梢血液検査（異常リンパ球，特に花細胞の有無が重要），生化学検査（特にLDH値，補正カルシウム値）を行う．次にCT，MRIやPET-CTなどの画像診断を用いて，深部のリンパ節や内臓浸潤の有無を検査する．

ATLLを発症すると，その約半数にATLL細胞の皮膚への浸潤，すなわち特異疹を合併してくる．特異疹で最も多いのが結節または腫瘤（33%）であり，次に全身性に生じる丘疹（22%）または紅斑（19%）と続く．慢性型やくすぶり型ATLLでは高頻度に皮膚病変を伴い，また，くすぶり型では末梢血中の異常リンパ球が少数か欠如している場合は，臨床的にMFと鑑別が困難な場合がある．特異疹では病理組織学的に，多型または分葉化した核を持つ中型～大型のT細胞が表在性またはびまん性に浸潤し，しばしば著明な表皮向性を示す．くすぶり型ATLLでは，真皮への浸潤はまばらで，あってもわずかに異型細胞を認めるだけの場合もある．腫瘍性T細胞は$CD3^+$，$CD4^+$，$CD8^-$の表現型を呈し，CD25は高頻度に陽性である．病理組織像でMFと鑑別できない場合もある．T細胞受容体はATLLもMFやSSもクローナルに再構成を認めるため鑑別にはならないが，ATLLではクローナル

役に立つ豆知識

わが国で開発された抗CCR4モノクローナル抗体療法はATLLに対する治験が終了し，2012年2月1日に厚生労働省がATLLの治療薬として承認しており，臨床での今後の使用が見込まれる．適応は化学療法後に再発または再燃した抗CCR4抗体陽性ATLLである．治験においても特異疹の改善が認められており，今後，期待される薬剤である．

なHTLV-1プロウイルスの組み込みが認められ，鑑別に有用である．また，表在リンパ節が腫脹している場合は，生検を行いATLL細胞の浸潤があるかどうかを確認する必要がある．

LDH値と可溶性IL-2R値はATLLの病勢をみる指標として重要である．急性転化し日和見感染症の合併が疑われる場合，β-Dグルカンは真菌感染症やニューモシスチス肺炎の有無や治療効果判定の指標となる．また，サイトメガロウイルス感染症が疑われる場合，血中サイトメガロウイルス抗原(C7-HRP)を測定すべきである．

治療の一般方針

皮膚病変を主体とする慢性型，くすぶり型や皮膚型ATLLでは，MFと同様に皮膚を標的とした局所療法（skin-directed therapy：SDT）が選択される．しかしSDTにより，必ずしもATLLの生命予後が改善されるわけではない．特異疹が紅斑や丘疹の場合，SDTとして副腎皮質ステロイド，抗癌薬の外用などが用いられるが，結節や腫瘤には効果が少なく，放射線（特に電子線）療法が選択される．特異疹が結節や腫瘤の場合，経過中に急性転化を生じ予後不良とされ，SDTに終始することなく，身体所見，採血，画像診断を含め病勢の悪化がないか注意深く観察し，急性転化の徴候あれば，単剤の化学療法薬を中心とした全身療法（systemic therapy：ST）へ切り替えていく必要がある．また，急性転化した場合は，後述の急性型，リンパ腫型ATLLと同様のSTが必要であり，前もって血液内科医と連携をとっておくことが肝要である．非特異疹として動物，真菌，細菌，ウイルスなどによる感染症を伴うことが多いので，感染症対策も必要である．

急性型，リンパ腫型ATLLでは，血液内科医と連携をとり多剤併用化学療法や同種造血幹細胞移植を中心としたSTが必要である．特に急性型ATLLでは高カルシウム血症を合併するので，補液，利尿薬，カルシトニン製剤，ビスホスホネート製剤などによりカルシウム値を下げると同時に，多剤併用化学療法を行う．さらに急性型ATLLでは，細胞性免疫の低下によるサイトメガロウイルス感染症やニューモシスチス肺炎などの真菌感染症を合併するため，抗ウイルス薬，抗真菌薬，ST合剤などの投与を併用する．

処方例

a．局所療法（SDT）

＜特異疹が紅斑，丘疹や局面の場合＞

①アンテベート軟膏：1日2回，外用

②紫外線療法（PUVA療法，ナローバンドUVB療法）：文献的には報告はあるが，筆者らは悪化した症例の経験があり施行していない．

③0.2% ACNUローション（ニドラン注）：1日2回，外用（保険適用外）．院内製剤として作成している．

＜特異疹が結節，腫瘤の場合＞

①ケナコルト-A：1%キシロカインで2～5倍に希釈し，結節や腫瘤に局注

②単発～数個の腫瘤であれば，電子線照射，計30～40 Gy程度

b．全身療法（ST）

①ラステット：50mg，分1～2，21日間内服し，1～2週間休薬する．これを1クールとして繰り返す．

②ペラゾリン細粒：1,600 mg，分1～2．5日間連続内服し，2～3週間休薬する．これを1クールとして繰り返す．

③プレドニゾロン：10～20 mg，分1～2，ラステットやペラゾリンの副作用予防として併用，また単独でも抗腫瘍効果が期待できる．

④(ニューモシスチス肺炎予防のため)バクタ：2～4錠，分2，週2回，連日内服

⑤(真菌症予防のため)ファンギゾンシロップ：24 mL，蒸留水などで500 mLに希釈し，毎食後に含漱

＜急性型，リンパ腫型ATLLの場合＞

血液内科医と連携をとり，多剤併用化学療法（modified LSG-15療法など），同種造血幹細胞移植［年齢や状態により，骨髄破壊的あるいは骨髄非破壊的移植（いわゆるミニ移植）を選択］を行う．特に後者は，移植医療の専門医がいる施設でないと施行できない．

生活指導

適度な睡眠をとり，規則的なバランスのとれた食事を摂ること，疲労を蓄積しないこと，また精神的ストレスを避け，精神的に安定した状態を保つことなどを指導している．

皮膚リンパ腫と鑑別すべき疾患，偽リンパ腫を中心に

天野　正宏　　瀬戸山　充

皮膚リンパ腫と鑑別すべき疾患は多岐にわたり，偽リンパ腫をはじめ，局面状類乾癬，多形皮膚萎縮，毛包性ムチン沈着症，光線性類細網症，薬疹/薬疹性リンパ節症，虫刺症と虫刺様反応，急性痘瘡状苔癬状粃糠疹，木村病，Weber-Christian 病，組織球貪食性脂肪織炎および反応性血球貪食，Wegener 肉芽腫，肥満細胞症，炎症性悪性線維性組織球腫，メルケル細胞癌，皮膚悪性腫瘍および転移性悪性腫瘍，Rosai-Dorfman 病などがあげられる[1]．ここでは偽リンパ腫を中心に皮膚悪性リンパ腫との鑑別点につき述べる．偽リンパ腫に関しては戸倉[2]や Ploysangam ら[3]の論文が詳しい．

偽リンパ腫とは

1891 年，Kaposi がその概念をはじめて報告し[1]，偽リンパ腫は良性の経過をたどるリンパ増殖性疾患であるが，原因も様々であり，その臨床像や経過も異なるヘテロな疾患群が含まれている．主な浸潤細胞の違いにより，大きく皮膚 T 細胞性偽リンパ腫と皮膚 B 細胞性偽リンパ腫に分けられ，皮膚 T 細胞性偽リンパ腫は浸潤細胞のパタンから帯状浸潤型と結節型に分けられる．皮膚 B 細胞性偽リンパ腫は結節型パタンのみを示す[3]（表 1）．また原因不明の皮膚 B 細胞性偽リンパ腫は，同義語として Cutaneous lymphoid hyperplasia，Lymphocytoma cutis（皮膚リンパ球腫），Lymphadenosis benigna cutis of Bäfverstedt（皮膚良性リンパ腺腫症），Pseudolymphoma of Spiegler-Fendt など様々な用語が用いられている．

原　因

偽リンパ腫の原因は，薬剤，刺青，虫刺，外傷，脱感作のための薬剤，金ピアス，ワクチン，鍼治療，ボレリア感染症，帯状疱疹，HIV 感染症，光線過敏のほか様々であり，原因が不明なこともある．皮膚 T 細胞性偽リンパ腫は薬剤が原因となる頻度が高く，原因薬剤としてはフェニトインが最も多い[3]．これに対し皮膚 B 細胞性偽リンパ腫は，しばしば原因不明のことが多い．

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疫　学

欧米の統計では皮膚 B 細胞性偽リンパ腫の男女比は 2：1 で男性に多く，白人対黒人比は 9：1，発症年齢中央値は 34 歳である[3]．一方，韓国では男女比 1：1 と性差はなく，発症年齢は平均 47.5 歳と報告されている[5]．*Borrelia Burgdorferi* 感染症にともなう偽リンパ腫は B 細胞性であり，主に欧州で報告されている．皮膚 T 細胞性偽リンパ腫は，発症率，有病率に関して，正確なデータや報告はない[3]．

臨 床 像

皮膚 B 細胞性偽リンパ腫は，病変は一般的に単発性の紅色結節として発生することが多く，顔面が好発部位である．病変は生検を契機に自然消褪することがある．皮膚 T 細胞性偽リンパ腫は，その原因により臨床像は多彩であり，一般的には多発性であり，全身性に病変を認めることもある．病変は原因が除去されない場合，進行性である[3]．

病理組織学的，分子生物学的検査

偽リンパ腫は浸潤細胞の組織学的パタンにより，帯状浸潤型と結節型に分けられる（表 1）．皮膚 T 細胞性偽リンパ腫は帯状浸潤型が主で，歯状息肉症などとの鑑別が必要となる．また皮膚 B 細胞性偽リンパ腫は結節型パタンがほとんどで，皮膚 B 細胞性リンパ腫が鑑別疾患として挙がる．病理組織学的には皮膚悪性リンパ腫との鑑別が重要であり，偽リンパ腫では① Polymorphous infiltrate，② Superficially located（top heavy）の特徴があり，特に B 細胞性偽リンパ腫では "grenz zone" の存在，また二次濾胞があれば中に tingible body macrophage の存在が挙げられる．これに対し皮膚悪性リンパ腫は① Monomorphous，dense infiltrate，② Deeply located（bottom heavy）である[6]．両者の鑑別は難しいこともあり，HE と免疫染色を比較し検討することが重要である．また T 細胞受容体（TCR）や免疫グロブリン重鎖（JH）遺伝子の再構成の有無は，両者の鑑別に役立つが，偽リンパ腫の中にも

表 1　皮膚偽リンパ腫の分類

皮膚 T 細胞性偽リンパ腫（CTPL）
帯状浸潤型 CTPL（major pattern）
Idiopathic CTPL
Lymphomatoid drug erupitin（most cases）
Nodular scabies（few cases）
Actinic reticuloid
Clonal CTPL
結節型 CTPL（minor pattern）
Anticonvulsant-induced pseudolymphoma syndrome（few cases）
Persistent nodular arthropod-bite reactions（most cases）
Nodular scabies（most cases）
Acral pseudolymphomatous angiokeratoma（most cases）
皮膚 B 細胞性偽リンパ腫（CBPL）（結節型パタン）
Idiopathic lymphocytoma cutis
Borrelial lymphocytoma cutis
Tatoo-induced lymphocytoma cutis
Post-herpes zoster scar lymphocytoma cutis
Lymphocytoma cutis induced by antigen injections/acupuncture
Persitent nodular arthropod-bite reactions（few cases）
Lymphomatoid drug eruptions（few cases）
Acral pseudolymphomatous angiokeratoma（few cases）
Clonal CBPL

文献 3）から改変
CTPL：cutaneous T-cell pseudolymphoma
CBPL：cutaneous B-cell pseudolymphoma

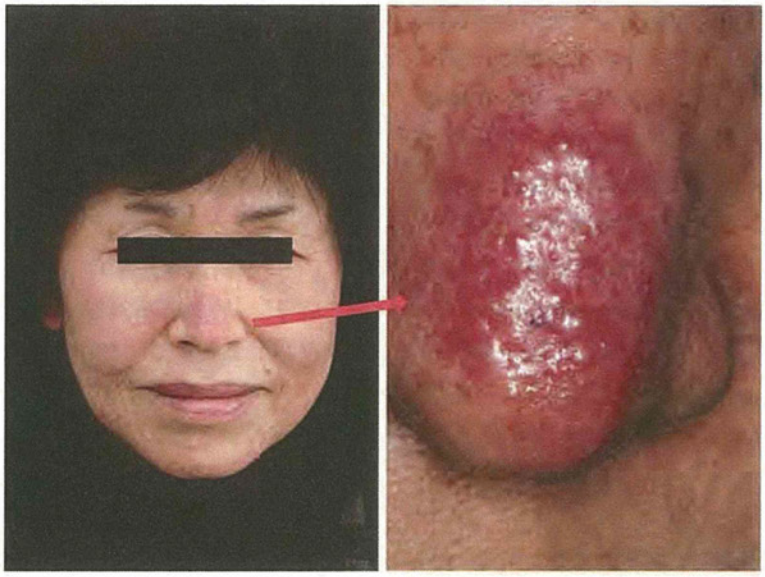

図　1

monoclonal な遺伝子再構成を認める報告もあり，注意が必要である[3]．

偽リンパ腫と皮膚悪性リンパ腫との関連

皮膚悪性リンパ腫に比べ，偽リンパ腫は臨床的には単発であり，自然消褪傾向を有し，潰瘍化はまれである[3]．しかし偽リンパ腫では皮膚悪性リンパ腫との鑑別が困難な症例もあり，臨床像はもちろん，病理組織像，免疫組織化学的染色，遺伝子再構成の結果を含め総合的に判断し，偽リンパ腫と診断したならば，長期観察して行くことで，皮膚悪性リンパ腫へ進展しないか留意する．Arai ら[7]は，偽リンパ腫と診断された 55 症例を再検討すると 4 症例（7.3%）が MALT リンパ腫であったという．また Baldassano ら[8]は病理組織学的に Marginal zone cell の存在や形質細胞の存在，B/T 細

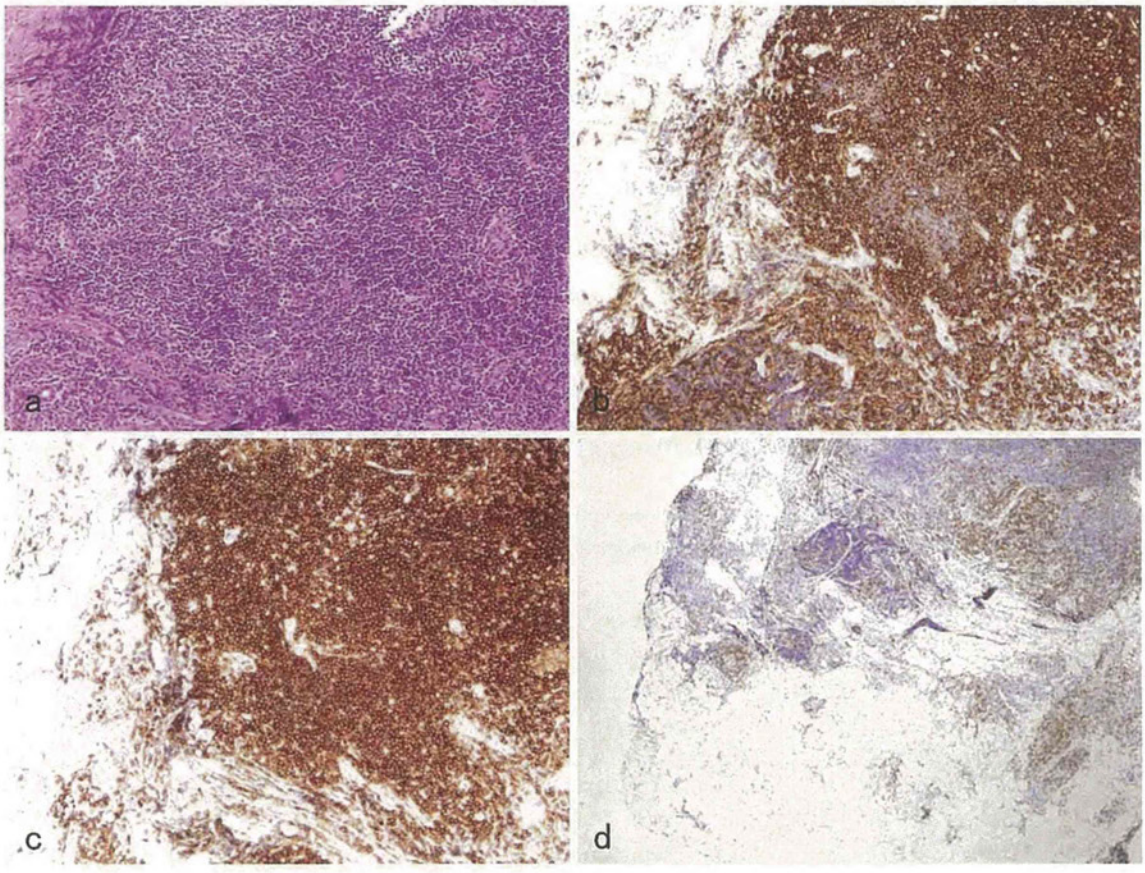

図 2

胞比が3以上，パラフィン切片でplasma cellの存在は，偽リンパ腫よりMALTリンパ腫と診断すべきとしている．Nihalら[9]は，偽リンパ腫44症例の中で2例が皮膚B細胞性リンパ腫へ進展したとしており，またAnandasabapathyら[10]も，偽リンパ腫と診断した46歳男性が4カ月後に再発し，びまん性大細胞型B細胞性リンパ腫と診断された症例を報告している．

治　療

原因となるものがあればそれを除去することが第一であり，特にT細胞性偽リンパ腫では薬剤が原因のこともあり，薬剤を中止することで病変は消褪する．また皮膚B細胞性偽リンパ腫の場合，生検が契機となり自然消褪することもある．病変が難治性，あるいは遷延性の場合，限局性病変であればコルチコステロイド外用または局注，液体窒素療法，インターフェロンα療法，局所放射線療法，外科的切除などが行われる．病変が広範囲に存在する場合，抗マラリア薬，光線化学療法あるいは，化学療法剤が用いられる[3]．

症　例

63歳，女性．

家族歴・既往歴：特記すべきことなし．

現病歴：初診の9カ月前から，鼻尖部に紅色の小丘疹が出現し，ステロイド外用薬にて加療するも拡大するため，当科を紹介された．

臨床像：充実性の小丘疹を伴う紅斑局面を認める（図1）．

検査所見：末梢血・生化学検査には異常なく，抗HTLV-1抗体陽性，可溶性IL2R値は正常，またヘリコバクターピロリIgG抗体値も正常であった．

病理組織像：真皮上層から皮下脂肪組織にかけて，結節状にリンパ球様細胞の浸潤を認める．それぞれの細胞には異型性はなく，付属器への浸潤も認めない（図2a）．

免疫組織学的染色：免疫染色ではB細胞が優位（図2b，c）で，反応性のリンパ球様細胞にはT細胞も染色される（図2d）．

経過および治療：皮膚B細胞性偽リンパ腫と診断し，トリアムシノロン局注を行ったところ，数カ月で消褪した．以後，再発を認めない．

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HTLV-1 uveitis

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Human T cell lymphotropic virus type 1 (HTLV-1) is the first retrovirus described as a causative agent of human disease. Following adult T cell leukemia/lymphoma and HLTV-1-associated myelopathy/tropical spastic paraparesis, HTLV-1 uveitis (HU) has been established as a distinct clinical entity caused by HTLV-1 based on seroepidemiological, clinical, and virological studies. HU is one of the most common causes of uveitis in endemic areas of Japan and can be a problematic clinical entity all over the world. HU occurs with a sudden onset of floaters and foggy vision, and is classified as an intermediate uveitis. Analysis of infiltrating cells in eyes with HU revealed that the majority of infiltrating cells were $CD3^+$ T cells, but not malignant cells or leukemic cells based on their T cell receptor usage. HTLV-1 proviral DNA, HTLV-1 protein, and viral particles were detected from infiltrating cells in eyes with HU. HTLV-1-infected $CD4^+$ T cell clones established from infiltrating cells in eyes with HU produced large amounts of various inflammatory cytokines, such as IL-1, IL-6, IL-8, TNF-α, and interferon-γ. Taken together, HU is considered to be caused by inflammatory cytokines produced by HTLV-1-infected $CD4^+$ T cells that significantly accumulate in eyes; therefore, topical and/or oral corticosteroid treatment is effective to treat intraocular inflammation in patients with HU. Further investigation is needed to establish a specific treatment for HU.

Keywords: HTLV-1, uveitis, ocular inflammation, $CD4^+$ T cell, T cell clone

INTRODUCTION

Retrovirus was first described in the 1970s (Temin and Baltimore, 1972), but its causal relationship with human diseases was not identified until the early 1980s when human T cell lymphotropic virus type 1 (HTLV-1) was identified as an etiologic agent of adult T cell leukemia/lymphoma (ATL; Poiesz et al., 1980; Hinuma et al., 1981; Yoshida et al., 1984). After the discovery of the link between HTLV-1 and ATL, HLTV-1 was also found to be a causal agent of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP; Gessain et al., 1985; Osame et al., 1986) and HTLV-1 uveitis (HU; Mochizuki et al., 1992a,b,c).

HTLV-1 uveitis, the third clinical entity of HTLV-1 infection, was established by a series of studies in the highly endemic area of southern Kyushu, Japan. Clinical case reports from this area suggested possible associations of HTLV-1 carriers with various ocular manifestations (Ohba et al., 1989). In the 1990s, the first set of evidence that indicated the causative implication of HTLV-1 in uveitis was reported by Mochizuki and colleagues. They showed clinical and laboratory data consisting of seroepidemiology, clinical features, detection of proviral DNA and mRNA of HTLV-1 from ocular tissues, and detection of viral particles from T cell clones (TCC) derived from the aqueous humor of the patient (Mochizuki et al., 1992a,b). Since then, it has been well established that uveitis is significantly related to HTLV-1. Here, we review historical findings that contributed to the establishment of the HU entity and recent advancements that deepen our understanding of HU.

SEROEPIDEMIOLOGY

HTLV-1 infection is known to have unique geographic distribution and is prevalent in Japan, Melanesia, the Caribbean Islands, Central America, South America, and Central Africa. It is estimated that 20 million people carry the virus worldwide (Watanabe, 2011). This virus is etiologically linked with HU, which is one of the most common causes of uveitis in the endemic area of Japan and can be a problematic clinical entity all over the world (Yoshimura et al., 1993; Takahashi et al., 2000; Merle et al., 2002; Pinheiro et al., 2006; Miyanaga et al., 2009). Uveitis is a sight-threatening inflammatory disorder affecting the intraocular tissues (Forrester, 1991) and is the third leading cause of blindness in developed countries. The etiology of uveitis is categorized as infectious or non-infectious and varies depending on the genetic background of the population and the prevalence of the pathogenic agent in the area. Clinically, the etiology of approximately 30% of cases could not be defined even when careful examinations were performed. A survey comparing the etiologies of uveitis in different areas of Japan demonstrated that the proportion of undefined etiologies was particularly high in southern Kyushu as compared to those in northern Kyushu and Tokyo. Seroepidemiological comparison studies (Mochizuki et al., 1992a,b; Shirao et al., 1993) in these highly endemic and non-endemic areas revealed that the HTLV-1 seroprevalence in patients with idiopathic uveitis was significantly higher than that in the following two control groups: patients with etiology-defined uveitis and patients with non-uveitic ocular diseases (**Figure 1**). This was the first clue suggesting that HTLV-1 infection is significantly related to uveitis. Uveitis is now recognized as a distinct clinical entity related to HTLV-1 and is designated as HU. The seroprevalence of HTLV-1 in the general Japanese population is known to have decreased after serological screening tests of HTLV-1 in blood donors started

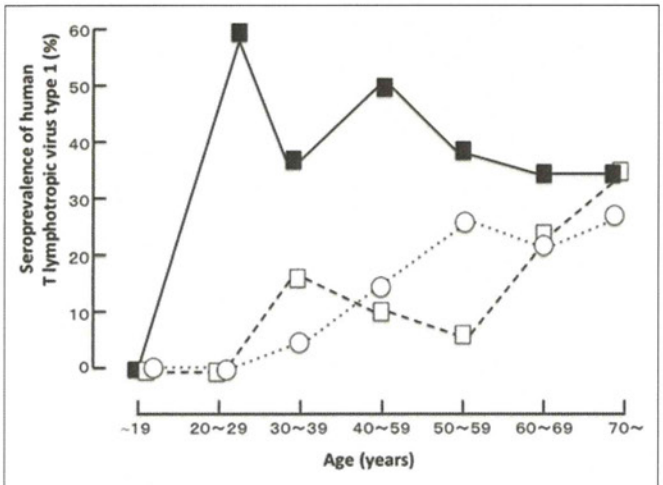

FIGURE 1 | The age distribution of the seroprevalence of human T cell lymphotropic virus type 1 in a highly endemic area (Miyakonojo, southern Kyushu, Japan; Shirao et al., 1993 with permission). ■, patients with idiopathic uveitis; □, patients with uveitis from a defined cause; ○, patients with non-uveitic ocular diseases.

in 1987, as blood transfusion and breastfeeding from mother to child are major routes of viral transmission (Iwanaga et al., 2009). A recent survey (Miyanaga et al., 2009) in the HTLV-1 endemic region revealed that the most common clinical entity was still HU, followed by Vogt–Koyanagi–Harada disease, sarcoidosis, and others. However, new cases of HU clearly decreased with time, while the prevalence of Vogt–Koyanagi–Harada disease and sarcoidosis has not changed much in the last two decades. The age distribution of HTLV-1 seroprevalence of all patients with uveitis including HU and of patients with uveitis excluding HU showed that the HTLV-1 seroprevalence increased with age in patients of both groups (Yoshimura et al., 1993; Takahashi et al., 2000; Miyanaga et al., 2009). As for the sex, higher prevalence rates were found in women, especially after 40 years of age. HTLV-1 is known to be transmitted by infected lymphocytes in sperm and this may contribute to the higher prevalence of the disease in women than in men (Yoshimura et al., 1993; Takahashi et al., 2000; Miyanaga et al., 2009). As for the prevalence of HU in different parts of the world, the prevalences of HU in Martinique (Merle et al., 2002) and Brazil (Rathsam-Pinheiro et al., 2009) are lower than that in Japan (Yamamoto et al., 1999; Pinheiro et al., 2006). In general, as migration to metropolitan areas is on the rise, the number of HTLV-1 carriers in metropolitan areas (for example, Tokyo) is significantly increasing (Uchimaru et al., 2008), although the number of carriers is still the highest in the endemic areas. In consideration of this evidence, it is estimated that the number of patients with HU is prospectively increasing in metropolitan areas. Therefore, careful examination concerning HU is needed for the diagnosis of uveitis.

CLINICAL MANIFESTATIONS

A recent report indicated that ocular disturbances may be the first manifestations of HTLV-1 infection to come to clinical attention, in addition to neurologic and rheumatologic signs and symptoms (Poetker et al., 2011). Therefore, all patients presenting for an initial diagnosis should be strictly screened for ocular symptoms. The major symptoms of HU at initial presentation are sudden onset of floaters, foggy vision, and blurred vision. Other symptoms are pain/burning, itching, and foreign body sensation. These symptoms appear in all geographic regions according to studies in Japan, Brazil, and Martinique (Yoshimura et al., 1993; Merle et al., 2002; Pinheiro et al., 2006). Regarding the anatomic diagnosis of uveitis according to the criteria of the International Uveitis Study Group, most patients had an intermediate degree of uveitis with moderate or heavy vitreous opacities (fine cells and lacework-like membranous opacities). The vitreous opacities were the most impressive findings and were accompanied by mild iritis and mild retinal vasculitis, but no uveoretinal lesions (Yoshimura et al., 1993). The ocular inflammation of HU was unilateral or bilateral (Yoshimura et al., 1993; Merle et al., 2002; Pinheiro et al., 2006). An association between HU and Graves' disease has been reported; HU occurs after the onset of Graves' disease in all cases (Yamaguchi et al., 1994). The most recent study (Miyanaga et al., 2009) reported a similar incidence of HU after Graves's disease as that reported by Yamaguchi et al. (1994). Only a few cases of HU develop into HAM/TSP, but no literature has reported that ATL develops in patients with HU during their clinical course. Further patient-tracking research is ongoing to determine whether HU is a risk factor for the development of ATL or HAM/TSP.

DIAGNOSIS

Considering seroepidemiological and clinical studies, the diagnosis of HU should be based on seropositivity for HTLV-1 with no systemic evidence of HTLV-1-related diseases (such as ATL or HAM/TSP) and exclusion of other uveitis entities with defined causes. Therefore, all clinical entities of uveitis with defined causes should be excluded by careful ophthalmic and systemic examinations. Patients with HU should not have ophthalmic and systemic symptoms that are compatible with other types of uveitis such as Behçet's disease, Vogt–Koyanagi–Harada syndrome, and sarcoidosis.

PATHOGENESIS

Eye research has progressed significantly in accordance with the development of modern molecular biological technology, such as the polymerase chain reaction and flow cytometry. Many fundamental findings have been obtained in the study of HU pathogenesis. The cells floating in the anterior chamber of the eye with HU consisted of lymphocytes with a small proportion of macrophages. No malignant cells or leukemic cells were detected in the aqueous humor of the patients with HU (Masuoka et al., 1995). The majority of infiltrating cells in the aqueous humor of patients with HU were $CD3^+$ T cells (Ono et al., 1997). Analysis by polymerase chain reaction of ocular-infiltrating cells revealed that HTLV-1 proviral DNA was detected in almost all patients with HU. However, proviral DNA was not detected in patients with uveitis of other defined etiology who were seropositive for HTLV-1. These data suggest that HTLV-1-infected cells are present at the local site of HU (Ono et al., 1997). Furthermore, expression of viral mRNA was detected by

reverse transcriptase-polymerase chain reaction from the inflammatory cells in the aqueous humor. More direct evidence of HTLV-1 in the pathogenesis of HU has been provided by using TCC derived from intraocular tissues of eyes with HU. Proviral DNA of HTLV-1 was identified in TCC from the ocular fluid (Sagawa et al., 1995). Immunohistochemical staining showed that HTLV-1 env and gag proteins were detectable in HTLV-1 provirus-positive TCC. Furthermore, electron microscopic observation of the TCC identified HTLV-1 virus particles, the mean diameter of which was 102 nm (Sagawa et al., 1995). Most HTLV-1-infected TCC had a $CD3^+CD4^+CD8^-$ phenotype and had polyclonal TCRα usage (Sagawa et al., 1995). The HTLV-1-infected TCC produced significant amounts of IL-1α, IL-2, IL-3, IL-6, IL-8, IL-10, TNF-α, IFN-γ, and GM-CSF, which are potent cytokines capable of inducing immune reactions and inflammation at the intraocular tissue level (Sagawa et al., 1995). These data suggest that cytokine production by HTLV-1-infected T cells in intraocular tissues is responsible for intraocular inflammation, i.e., uveitis (**Figure 2**). In addition to this molecular biological/immunological evidence, virological research supported the pathogenicity of HTLV-1 in the eye by the following three pieces of evidence: (1) the HTLV-1 provirus load in patients with HU is significantly higher than that in asymptomatic carriers without uveitis (Ono et al., 1995); (2) the proviral load in peripheral blood mononuclear cells correlates with the intensity of intraocular inflammation (Ono et al., 1998); and (3) the proviral load in the eyes of patients with HU is significantly higher than that present in peripheral blood mononuclear cells (Ono et al., 1997). Serologic data showed that the antibody level against HTLV-1 in patients with HU was similar to that in asymptomatic carriers of HTLV-1, but was lower than that in patients with HTLV-1-associated myelopathy (Mochizuki et al., 1992b). Antibody to the virus in the aqueous humor was also detected in all tested samples from patients with HU. Flow cytometry analysis indicated that the CD4 fraction was elevated and the CD8 fraction was decreased in peripheral lymphocytes from patients with HU, thereby elevating the CD4/8 ratio in the HU group as compared with the seronegative group. Furthermore, the CD25 fraction of T lymphocytes with expression of interleukin 2 receptors was significantly elevated in patients with HU. The serum levels of soluble interleukin 2 receptors (sIL2R or sCD25) were also significantly higher in patients with HU than in seronegative healthy controls (Yoshimura et al., 1993). Taken together, these laboratory data suggest that the immune-mediated mechanism, particularly involving $CD4^+$ T cells, plays a critical role in the pathogenesis of HU.

THERAPY

Immunopathogenesis studies of HU showed that the majority of ocular-infiltrating cells are inflammatory cells, but not malignant cells. Also, a series of studies showed that HU is caused by inflammatory cytokines produced by HTLV-1-infected $CD4^+$ T cells that significantly accumulate in the eyes of the patients. Furthermore, the addition of corticosteroids in the culture medium suppressed the cytokine production (Sagawa et al., 1995). Therefore, corticosteroid treatment is effective for treating the intraocular inflammation of patients with HU by suppressing the cytokine production of HTLV-1-infected $CD4^+$ T cells. Clinical management should be performed according to the degree of ocular inflammation. HU with a mild degree of ocular inflammation can be managed by topical non-corticosteroidal or corticosteroidal anti-inflammatory drugs. A sub-Tenon's injection of corticosteroids may be used when the patients have moderate inflammatory activity in the vitreous cavity. If the vitreous inflammatory activity and the retinal vasculitis are severe, oral corticosteroids should be given, but the long-term administration of a systemic corticosteroid should be avoided. In most cases, intraocular inflammation is markedly improved with these therapies and complete remission is achieved. The visual prognosis for cases of HU is generally good with these corticosteroid treatments, although approximately 60% of patients experience recurrences of uveitis (Yoshimura et al., 1993).

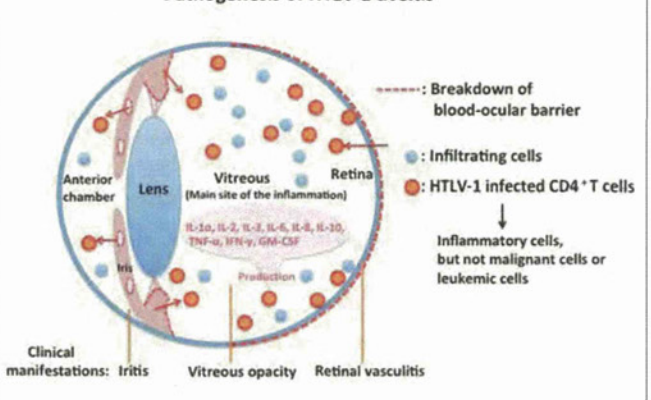

FIGURE 2 | The majority of infiltrating cells in eyes with HTLV-1 uveitis are inflammatory cells and not malignant or leukemic cells. HTLV-1 uveitis is caused by inflammatory cytokines produced by HTLV-1-infected $CD4^+$ T cells that significantly accumulate in the eyes of patients.

CONCLUSION

We reviewed the seroepidemiological, clinical, molecular biological, and virological studies that established the HU entity and clarified the immunopathogenesis and the clinical management of HU. Corticosteroid is the only effective treatment for HU to suppress the cytokines produced by infiltrating HTLV-1-infected cells; however, it is unknown whether long-term corticosteroid treatment adversely affects patients with HU. Many mechanisms in HU remain unclear, such as how HTLV-1-infected $CD4^+$ cells break down the ocular blood barrier and why the vitreous humor is the major site of inflammation (**Figure 2**). We may be able to find more effective treatments if we can understand the mechanism of HU in more detail. Recent studies have shown new insights into HTLV-1 infection and pathogenesis by pursuing the molecular functions of HTLV-1 basic leucine zipper factor and Tax (Yasunaga and Matsuoka, 2011). However, few studies have been conducted to apply these new findings to HU research. Further investigation is needed to establish a specific treatment for HU. HU results from HTLV-1 infection; therefore, the most important means of preventing this disease is by spreading the knowledge about HTLV-1.

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REVIEW

HTLV infection and the eye

Koju Kamoi and Manabu Mochizuki

Purpose of review
Human T-cell lymphotropic virus (HTLV) is the first discovered retrovirus causing malignancy in human. HTLV infection affects host's ocular tolerance and causes various diseases in the eye. Here we discuss the manifestations, mechanisms, treatments, and future directions of HTLV-related ocular diseases.

Recent finings
Recent serological researches showed that the number of HTLV-1 carriers in metropolitan area was increasing, although seroprevalence of HTLV-1 in general population was decreased after screening serological tests in blood donors started. The most common clinical entity of uveitis was still HTLV-1 uveitis in HTLV-1 highly endemic area, but prevalence of HTLV-1 uveitis varies in different parts of the world. As for treatment of inflammation, tacrolimus and 5-azacytidine were reported to be effective for autoimmune manifestations in HTLV-1-related overlap syndrome (deratomyositis/Sjogren's syndrome) and HTLV-1-related myelodysplastic syndrome. Interleukin-2 receptor targeted therapies improved scleritis in patients with adult T-cell leukemia/lymphoma caused by HTLV-1. Basic researches identified that HTLV-1 tax and HTLV-1 basic leucine zipper factor play critical roles in the HTLV-1-related disease and are now being investigated as targeted therapies.

Summary
Development of modern molecular biology makes it possible to reveal deep insights of HTLV-1-related ocular diseases. Although effective therapies based on basic researches have been reported, further endeavor is necessary to establish much more specific treatments of the ocular diseases.

Keywords
adult T-cell leukemia/lymphoma, Keratoconjunctivitis sicca, HTLV-1 basic leucine zipper factor, HTLV-1 tax, HTLV-1 uveitis

INTRODUCTIONS

Retrovirus is a RNA virus encoding for a reverse transcriptase, which translate the viral RNA into a DNA provirus, which in turn is rapidly incorporated into the host's genome [1]. Retroviruses are currently classified into oncoviruses and lentiviruses. Oncoviruses are associated with haematological proliferations and tumours of connective tissues in animal species. Human T-cell lymphotropic viruses (HTLVs) are the representative viruses and HTLV-1 was the first retrovirus described as a causative agent of human disease [2,3]. Lentivirus induces chronic and progressive pulmonary and/or neurological diseases in animal species. The representative virus in human is HIV, which was previously named HTLV-3 and now reclassified into HIV and is a causative agent of AIDS [1].

Human retrovirus (HTLV/HIV) infection affects on host's ocular tolerance, which results in various diseases, particularly uveitis [4–6]. Although HIV-related ocular manifestations are well known among ophthalmologists, their knowledge of HTLV-related ocular manifestation seems to be insufficient. The information of HTLV infection is now important because a recent survey indicates that HTLV-1 carriers are estimated to spread from local endemic areas to nonendemic metropolitan areas [7]. Therefore, we believe that this review of HTLV might be enough for ophthalmic practice and hope that this might highlight scientific attention to HTLV-1 infection among ophthalmologists.

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KEY POINTS

- HTLV-1 carriers are estimated to spread from local endemic areas to nonendemic metropolitan areas.
- HTLV-1 ocular manifestations can be mainly classified into three groups, uveitis, opportunistic infection/malignant infiltration of the eye in ATL patients and keratoconjunctivitis sicca.
- The most frequent ocular manifestation of HTLV-1 infection that ophthalmologists should keep in mind is HTLV-1 uveitis.
- HTLV-1 tax and HTLV-1 basic leucine zipper factor (HBZ) are thought to be responsible for immune dysregulation and may contribute to ocular manifestations.

HUMAN T-CELL LYMPHOTROPIC VIRUS INFECTION AND SEROLOGY

Retrovirus was first described in 1970s [8], but the causal relationship with human diseases was identified in the early 1980s when HTLV-1 was identified as a causative agent of adult T-cell leukemia/lymphoma (ATL) [2,3]. After the discovery of HTLV-1, related viruses have been isolated and HTLV is now composed of four related HTLVs, that is HTLV-1 to HTLV-4 [9]. However, only HTLV-1 has been obviously linked to human diseases at present.

HTLV-1 infection is known to have unique geographic distribution, and is prevalent in southern part of Japan, Melanesia, the Caribbean Islands, Central and South America, as well as central Africa. It is estimated that 20 million people carry the virus worldwide [10]. The current survey indicated that the seroprevalence of HTLV-1 in general population (in Japan) is known to be decreased after screening serological tests of HTLV-1 in blood donors started in 1987 because blood transfusion and breastfeeding from mother to child are major routes of the viral transmission [11]. However, another survey indicated that the number of HTLV-1 carriers in the metropolitan area is significantly increasing because of migration from the endemic areas to the metropolitan areas [7]. Therefore, ophthalmologists, especially in the metropolitan area, are required to know HTLV-related ocular manifestation to avoid misdiagnosis.

OCULAR MANIFESTATIONS IN HUMAN T-CELL LYMPHOTROPIC VIRUS-1 INFECTION

A recent report indicated that ocular complains were the first manifestation of HTLV-1 infection to come to clinical attention, in addition to neurologic and rheumatologic complains [12]. The most frequent ocular manifestation of HTLV-1 infection that ophthalmologists should keep in mind is HTLV-1 uveitis [13]. HTLV-1 uveitis is now recognized as the third clinical entity of HTLV-1 infection following ATL and HTLV-1-associated myelopathy/tropical spastic paraparesis [14–16]. Clinical entity of HTLV-1 uveitis was established by a series of research conducted by Mochizuki *et al.* in 1990s. They showed clinical and laboratory data consisting of seroepidemiology, clinical features, detection of proviral DNA and mRNA of HTLV-1 from ocular tissues, and detection of viral particles from T-cell clones (TCCs) derived from the aqueous humor of the patient [4,5]. Since then, it has been well established that uveitis is significantly related to HTLV-1. In addition to HTLV-1 uveitis, many other ocular manifestations, which are proved linkage to HTLV-1 infection, have been reported all over the world. Taken together, HTLV-1 ocular manifestations can be mainly classified into three groups, uveitis, opportunistic infection/malignant infiltration of the eye in ATL patients and keratoconjunctivitis sicca (KCS).

HUMAN T-CELL LYMPHOTROPIC VIRUS-1 UVEITIS

Seroepidemiological comparison study [4,5,17] in endemic/nonendemic area revealed that the HTLV-1 seroprevalence in patients with idiopathic uveitis was significantly higher than that in following two control groups: patients with cause defined as uveitis and patients with nonuveitic ocular diseases. This was the first clue suggesting that HTLV-1 infection is significantly related to uveitis. The uveitis is now recognized as a distinct clinical entity related to HTLV-1 and designated as HTLV-1 uveitis.

Recent survey [18] in the endemic area revealed that the most common clinical entity of uveitis was still HTLV-1 uveitis, followed by Vogt–Koyanagi–Harada (VKH) disease, sarcoidosis and others. However, the new patients of HTLV-1 uveitis clearly decreased with time, although VKH disease, sarcoidosis and others do not have changed much in the last two decade. As for the prevalence of HTLV-1 uveitis in different parts of the world, the prevalence of HTLV-1 uveitis in Martinique [19], and that of HTLV-1 uveitis in Brazil are lower than that reported in Japan [20,21]. HTLV-1 uveitis's major symptoms at initial presentation were sudden onset of floater, foggy vision and blurred vision. Other complains are pain/burning, itching and foreign body sensation. Most patients had an intermediate uveitis with moderate or heavy vitreous opacities (fine cells and lacework-like membranous opacities). The vitreous opacities were the most impressive findings and were accompanied by mild iritis and mild

retinal vasculitis but no uveoretinal lesions [22]. The ocular inflammation of HTLV-1 uveitis was unilateral or bilateral [19,20,22]. Interesting observation was reported in HTLV-1 uveitis patients that was an association with Graves' disease. HTLV-1 uveitis occurred after the onset of Graves' disease in all cases [23]. The incidence of HTLV-1 uveitis after Graves' disease in the first report was very similar to that of the latest [18].

As for the mechanism of HTLV-1 uveitis, analysis of infiltrating cells in the eye with HTLV-1 uveitis revealed that the majority of infiltrating cells were $CD3^+$ T cells, but not malignant cells or leukemic cells based on their T-cell receptor usage [24]. HTLV-1 proviral DNA, HTLV-1 protein and viral particle were detected from ocular infiltrating cells in the eye of HTLV-1 uveitis patients [4,5]. A series of researches showed that HTLV-1 uveitis was caused by inflammatory cytokines produced by HTLV-1-infected $CD4^+$ T cells that are significantly accumulated in the eye of the patients. HTLV-1-infected $CD4^+$ TCCs established from infiltrating cells in eyes of HTLV-1 uveitis patients produced a large amount of various inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8, tumour necrosis factor (TNF-α) and interferon (IFN)-γ [25]. Furthermore, addition of corticosteroids in the culture medium suppressed the cytokine production [26].

ADULT T-CELL LEUKEMIA/LYMPHOMA-RELATED OCULAR SYMPTOM

Opportunistic infection and malignant infiltration of the eye are main ophthalmic features of ATL patients. The representative opportunistic infection in the eye is cytomegalovirus retinitis [27]. Cytomegalic cell infiltration and accompanied retinal necrosis can be seen. This ocular manifestation is similar to that of patients with AIDS, and is also associated with poor prognosis. Many case reports indicate that HTLV-1-infected leukocytes can infiltrate into the almost all tissue in the eye, which cause various ocular manifestations in such areas as orbita, cornea, iris, lens, vitreous, uvea, retina, sclera, optic nerve [28]. In addition to these regions, choroidal manifestation was newly reported and identified as a distinct ocular manifestation of ATL patient [28].

Investigation of the eye in HTLV-1-infected patients has progressed significantly in accordance with development of modern molecular biology technology such as microdissection, PCR, cytokine detection system and Flow cytometry. ATL cells are characterized by the expression of IL-2 receptor alpha (IL-2Rα) (CD25), which is not expressed in normal resting T cells. The recent technology showed that elevated levels of soluble IL-2Rα may suggest direct ocular infiltration of ATL cells, as ATL cells secrete soluble forms of IL-2Rα into the vitreous [28]. Detection of soluble IL-2Rα in vitreous may be a cue of ocular infiltration and prognosis [29].

KERATOCONJUNCTIVITIS SICCA

KCS is usually a part of Sjögren's syndrome. HTLV-1-associated tear film changes were first reported when investigating mice expressing the *Tax* gene and developing a Sjögren's syndrome -like clinical symptom [30]. The association between Sjögren's syndrome and HTL V-1 in humans was found in an endemic zone higher prevalence of this virus among the carriers of the syndrome than in the seronegative control group [31]. Development of clinical Sjögren's syndrome manifestations in HTL V-1 carriers have been explained by the activated autoreactive T cells, which break immunological tolerance and result in Sjögren's syndrome. However, KCS associated with HTLV-1 infection might differ from ocular manifestation in primary or secondary Sjögren's syndrome because it does not reveal immunological alteration related to a rheumatologic disease [19,32–34]. Therefore, the mechanism of HTLV-1-associated Sjögren's syndrome is still controversial. However, some patients have more than one of these HTLV-1-associated inflammatory conditions, that is overlap syndrome. HTLV-1 infection can change immunological status by T cell activation and various cytokines, which may contribute to the development of overlap syndrome. Infected activated T cells are thought to proliferate and infiltrate into not only the eye [26] but also other organs and secrete a variety of cytokines, including IL-1, IL-2, IL-3, IL-6, TNF-α and IFN-γ [35]. For example, a report presented that a HTLV-1 carrier had clinical and pathological features of overlap syndrome, which consisted of Sjögren's syndrome and dermatomyositis.

TREATMENT OF HUMAN T-CELL LYMPHOTROPIC VIRUS-1-RELATED OCULAR MANIFESTATION

HTLV-1 uveitis is considered to have caused by inflammatory cytokines produced by HTLV-1-infected $CD4^+$ T cells, which significantly accumulated in the eye of the patients, and, therefore, topical and/or oral corticosteroid treatment is effective to treat HTLV-1 uveitis patients by suppressing cytokine production of HTLV-1-infected $CD4^+$ T cells for their intraocular inflammation [4,5,13]. Clinical management should be performed according to their degree of ocular inflammation. HTLV-1