

Brief Report

HTLV-II–ASSOCIATED CUTANEOUS T-CELL LYMPHOMA IN A PATIENT WITH HIV-1 INFECTION

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PATIENTS infected with human immunodeficiency virus type 1 (HIV-1) are susceptible to neoplasms, including Kaposi's sarcoma, non-Hodgkin's lymphoma, and anal and cervical carcinoma.¹⁻⁵ Some of these neoplasms have been associated with oncogenic infectious agents such as human herpesvirus 8 (HHV-8), Epstein-Barr virus (EBV), human T-cell leukemia-lymphoma virus type I (also known as human T-cell lymphotropic virus type I; HTLV-I), and the human papillomavirus (HPV).¹⁻⁵ Presumably, the immunosuppression caused by HIV-1 allows for the expansion of virally transformed cells and the development of cancer.

HTLV-I and human T-cell lymphotropic virus type II (HTLV-II) are oncogenic retroviruses.^{6,7} HTLV-I infects CD4+ T cells and, to a lesser extent, CD8+ T cells and B cells.^{3,8} It is the cause of adult T-cell leukemia-lymphoma.^{6,9} Persons with asymptomatic HTLV-I infection have heightened immune reactivity, whereas those with adult T-cell leukemia-lymphoma do not, which suggests that there may be immunologic regulation of transformed T-cell expansion.¹⁰ HTLV-II, which is especially prevalent among intravenous drug abusers in the United States,¹¹ is associated with clonal expansion of T cells, with the in-

fecting cells being predominantly CD8+ T lymphocytes.¹²⁻¹⁵ HTLV-II has also been associated with rare T-cell cancers that are usually of the CD8+ phenotype.^{7,16,17}

Infection with both HIV-1 and HTLV-I or HTLV-II occurs in a sizable minority of intravenous drug abusers in the United States.¹¹ Although data are conflicting about whether the prognosis for a patient with HIV-1 infection is worse when the patient is also infected with HTLV-I, most reports on infection with both HIV-1 and HTLV-II suggest a better prognosis than for infection with HIV-1 only.^{18,19} However, two cases have been reported of patients with both HTLV-II and HIV-1 infection who had severe T-lymphocytic infiltration of skin, eosinophilia, and dermatopathic lymphadenopathy.²⁰ In one of these patients, the infiltrating T lymphocytes were found to be CD8+CD4-. The phenotype of the other patient's cells was not determined. In addition, neither patient's tissues were evaluated for T-cell-receptor gene rearrangements or HTLV-II to prove the clonality of the lymphocytic infiltrations and the involvement of HTLV-II in the pathogenesis of the skin disease. We describe a patient infected with both HIV-1 and HTLV-II in whom we diagnosed a clonal CD3+CD8+CD4- cutaneous T-cell lymphoma that was positive for HTLV-II.

CASE REPORT

A 38-year-old febrile black man who had lived his entire life in the United States was referred to the oncology clinic of the State University of New York Upstate Medical University in Syracuse with a diffuse, generalized, finely desquamative, and intensely pruritic erythrodermatitis. His skin had no plaques or nodules and was secondarily infected in areas of excoriation. He had no adenopathy or organomegaly.

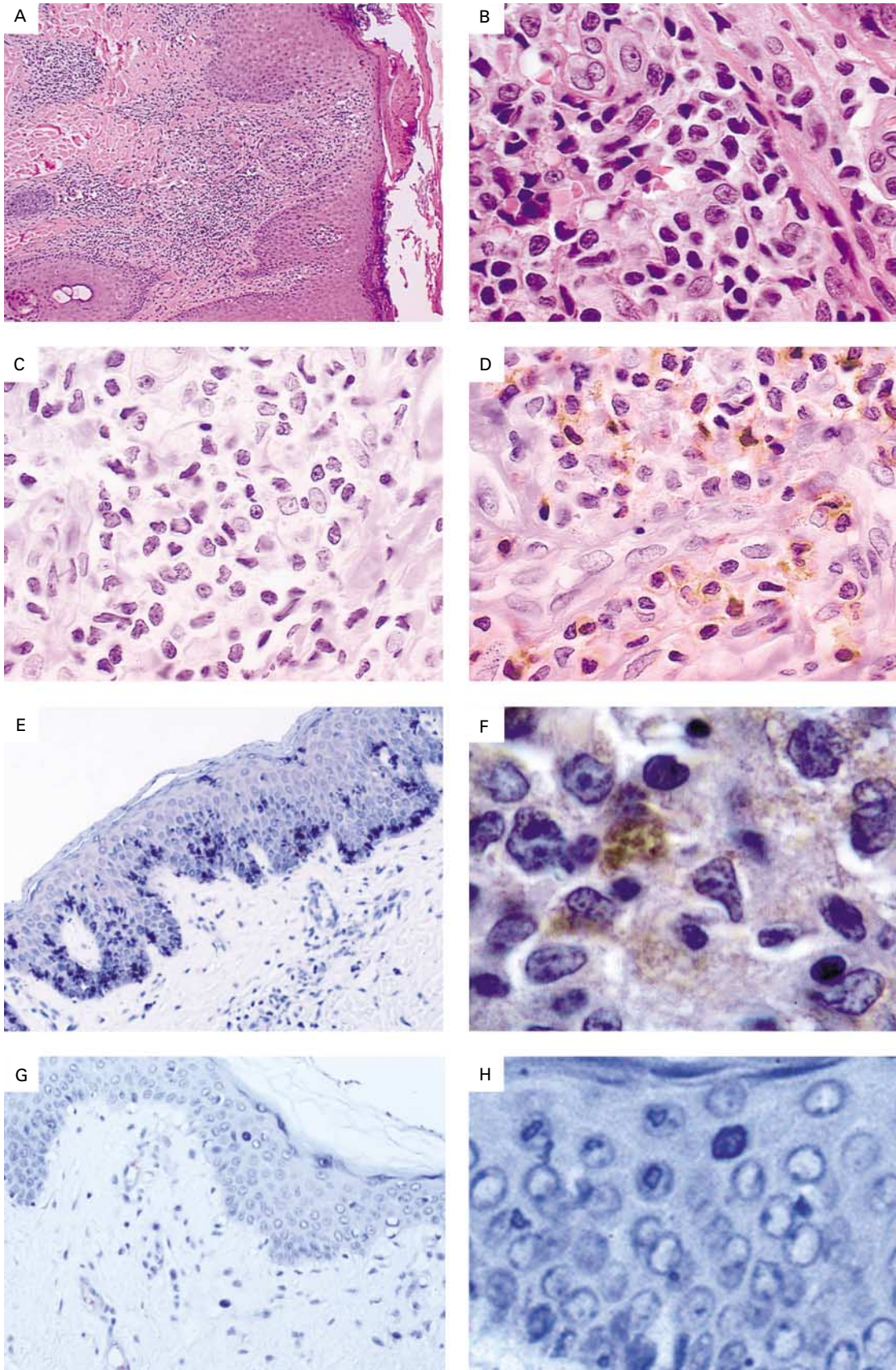
The patient was an intravenous drug abuser known to have been infected with HIV-1 for two years. His medications at the time, which was before the Food and Drug Administration's approval of HIV-protease inhibitors, included zidovudine, trimethoprim-sulfamethoxazole, and diphenhydramine hydrochloride. The first two drugs were discontinued, but the patient had no relief of symptoms. Cultures of the patient's blood and skin grew *Staphylococcus aureus*, which responded to treatment with intravenous cefazolin sodium. The patient's skin biopsies were diagnostic for a CD8+CD4- cutaneous T-cell lymphoma. He was treated with cyclophosphamide (200 mg orally on days 1, 3, and 5 for three 3-week cycles), methotrexate (20 mg orally on days 1 and 3 for three 3-week cycles), and prednisone (100 mg orally on days 1 through 5 for three 3-week cycles). He was also treated with concomitant total-body electron-beam irradiation (total dose, 40 Gy). In response to this therapy, the pruritus resolved and the erythroderma and exfoliation decreased. However, the patient declined further ther-

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Figure 1 (facing page). Sections of the Patient's Skin Showing Intense Dermal and Epidermal Infiltration by Lymphocytes.

Panel A (×200) and Panel B (×1000) show the results of staining with hematoxylin and eosin. Immunostaining for CD4 (Panel C) and CD8 (Panel D) (both ×1000) indicated a CD8+CD4- cutaneous T-cell lymphoma. Immunostaining for HTLV-I and HTLV-II gp46 env proteins (Panel E, ×400) and gag p24 proteins (Panel F, ×2000) was positive in a substantial minority of lymphocytes throughout the infiltrate. Normal skin from a person without HIV or HTLV infection that was stained for HTLV-I and HTLV-II gp46 env (Panel G, ×500) and p19 (Panel H, ×2000) is shown as a negative control. (Panels C through H, hematoxylin background stain.)



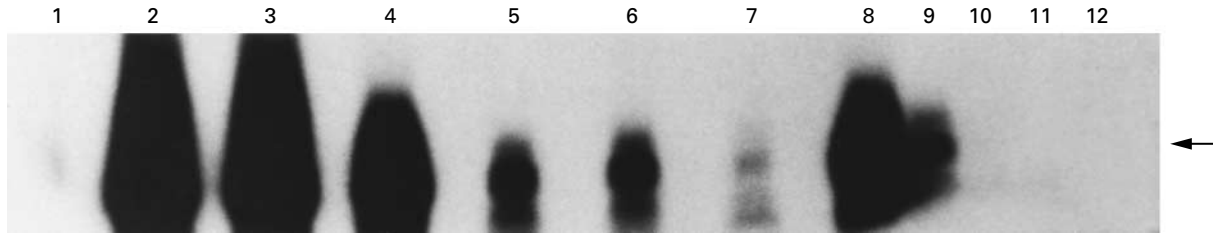
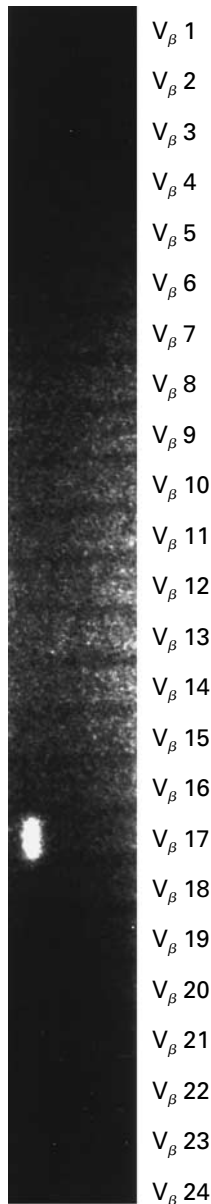


Figure 2. Autoradiograph of a Southern Blot of DNA Amplified with the HTLV-I and HTLV-II tax Primer Pair SK43 and SK44 and Probed with the ³²P-Labeled HTLV-I and HTLV-II Oligonucleotide SK45.

Lane 1 shows the primer-only control (no DNA added); lanes 2 through 7 show serial dilutions of DNA from the patient's lymphomatous skin lesion, ranging from 100,000 cells (lane 2) to 1 cell (lane 7) (1 μg of DNA is assumed to equal 150,000 cells); lanes 8 through 11 show 100, 10, 1, and 0.1 copies, respectively, of HTLV-II-positive control DNA; and lane 12 shows blood from an uninfected volunteer donor as a negative control. The arrow indicates the expected 159-bp size of the amplified product.



apy and died one year later at another institution from toxoplasmosis and with recurrence of cutaneous T-cell lymphoma.

METHODS

Skin Biopsy

Formalin-fixed biopsy specimens were taken from areas of active erythroderma in the skin. DNA was extracted with organic solvents from the skin and analyzed for HIV-1, HIV-2, HHV-8, HPV, EBV, HTLV-I, and HTLV-II DNA and rearrangements of the T-cell-receptor V_{β} and V_{γ} genes by the polymerase chain reaction (PCR) with use of previously described primers and probes.^{3,13,21-23} Amplified HTLV-I and HTLV-II *pol* DNA was detected with use of a solid-phase assay (Cellular Products, Buffalo, N.Y.).²³ All other analyses were performed with the Southern blot technique or ethidium bromide gel with electrophoresis. Sections of the paraffin-embedded skin tissue were stained with hematoxylin and eosin and were examined for lymphocyte cell-surface markers of HTLV-I and HTLV-II infection with use of murine monoclonal antibodies to CD3 and CD20 (Dako, Carpinteria, Calif.), CD4 and CD8 (Novo Castra, Vector, Burlingame, Calif.), CD45RO (Zymed, San Francisco), and HTLV-I and HTLV-II p19 gag, p24 gag, and gp46 env proteins (Cellular Products) with use of a streptavidin-biotin-peroxidase technique after the retrieval of antigen with citrate buffer.²⁴⁻²⁶ Irrelevant isotype-specific murine monoclonal antibodies and normal skin from a person without HIV-1, HIV-2, HTLV-I, or HTLV-II infection were used as negative controls.

Peripheral Blood

Peripheral blood was tested for antibodies to HIV-1 or HIV-2 and HTLV-I or HTLV-II with use of enzyme-linked immunosorbent assays (Cellular Products).¹¹ Seropositivity and discrimination between HTLV-I reactivity and HTLV-II reactivity were confirmed by analyses in DBL 2.2 (HIV) and DBL 2.3 (HTLV-I and HTLV-II) Western blot assays (Cellular Products).²⁷ Phenotypic cell-surface markers on peripheral-blood mononuclear cells were also analyzed.³ DNA was extracted from the peripheral blood and analyzed by PCR for HIV-1, HIV-2, HHV-8, EBV, HTLV-I, and HTLV-II DNA and T-cell-receptor V_{β} and V_{γ} gene rearrangements. The peripheral blood was also analyzed by Southern blotting for T-cell-receptor gene rearrangements and HTLV-I and HTLV-II DNA.³

Establishment and Characterization of a T-Cell Line Derived from the Peripheral Blood

The patient's peripheral-blood mononuclear cells were cultured without activation of phytohemagglutinin in RPMI 1640 medium, 10 percent fetal-calf serum, and 10 percent delectinated, partially purified interleukin-2 (Cellular Products), augmented with 20 U of recombinant interleukin-2 per milliliter (Cellular Products).⁶ No additional fresh

Figure 3. An Ethidium-Stained Gel of the Amplified Products after DNA from the Patient's Skin Was Subjected to the Polymerase Chain Reaction with 24 Different Sets of Primers That Target Each of the 24 Families of Rearranged T-Cell-Receptor V_{β} Genes.

Family 17 is clonally expanded.

uninfected cells were added. The culture was continued for up to one year before being frozen. During that period it was assessed for the expression of reverse transcriptase, retrovirus particles, and the production of HIV-1 p24, HTLV-I and HTLV-II p19, and gp46; the content of HIV-1, HTLV-I, and HTLV-II DNA by PCR and Southern blot analysis; and for cell-surface lymphocyte markers and T-cell-receptor gene rearrangements by Southern blot analysis and PCR.^{6,25,26}

RESULTS

The patient's skin-biopsy specimen showed intense dermal infiltration by lymphocytes, many of which had convoluted nuclei (Fig. 1). This process extended into the epidermis, and some collections were suggestive of Pautrier's microabscesses (Fig. 1). Phenotypic analyses showed that most of these cells were CD3+CD8+CD45RO+CD4-CD20- (Fig. 1 and data not shown). A substantial minority of the lymphocytes were positive for HTLV-I and HTLV-II p19, p24, and gp46 antigens (Fig. 1). DNA from the skin was positive for HTLV-II but not HIV-1, HIV-2, HTLV-I, EBV, HHV-8, or HPV (Fig. 2 and data not shown). The sample was positive for all HTLV-II

primer pairs used, which included those targeted at the HTLV-II LTR (long terminal repeat), *pol*, *env*, and *tax* regions. The DNA also contained a clonal expansion of T cells as determined by PCR for both rearrangements of the T-cell-receptor genes V_{β} and V_{γ} . The V_{β} clonotypic family 17 was expanded (Fig. 3). Quantitative PCR indicated that the number of copies of HTLV-II DNA and V_{β} clonotype 17 DNA each approached 1 per cell (Fig. 2 and data not shown).

The patient's peripheral blood was positive for antibodies to HIV and HTLV by enzyme-linked immunosorbent assay. Western blots were positive for antibodies to both viruses and indicated anti-HTLV-II rather than anti-HTLV-I seroreactivity (Fig. 4). The peripheral blood contained 140 CD4+ T lymphocytes per cubic millimeter (normal, 350 to 1600) and 880 CD8+ T lymphocytes per cubic millimeter (normal, 220 to 1000). No cells that were positive for HTLV-II p19 gag, p24 gag, or gp46 env antigen were detected. DNA extracted from the cells was negative in a Southern blot assay for HTLV-II; it was positive

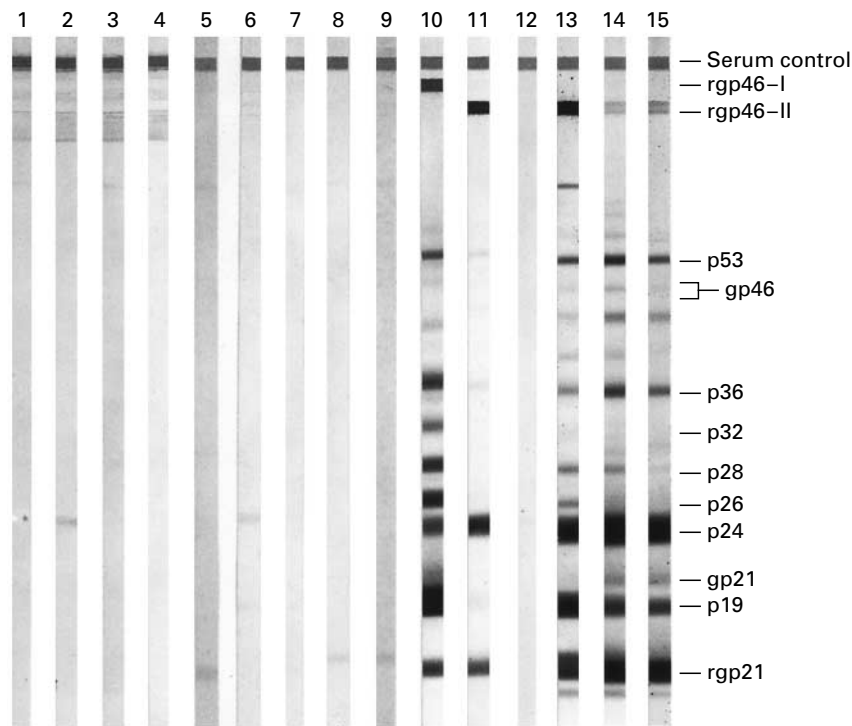


Figure 4. DBL 2.3 Western Blot Confirming That the Patient Was Positive for Antibodies to HTLV-II.

The first nine strips show serum samples from HTLV-uninfected negative controls. The 10th and 11th strips show serum samples that are positive controls for HTLV-I and HTLV-II, respectively, and the 12th strip shows another negative control. Strips 13, 14, and 15 show plasma collected at different times from our patient with CD8+ cutaneous T-cell lymphoma. All his samples reacted with the HTLV gag proteins p24 and p19 and their polyprotein precursors and with the HTLV env proteins gp21, rgp21, and gp46. The patient's serum samples reacted specifically with the HTLV-II gp46 recombinant env peptide (rgp46-II), but not the HTLV-I gp46 recombinant env peptide (rgp46-I). His serum samples were therefore confirmed to have reactivity to HTLV-II.

	4757	GCC	TGG	TCG	AGA	GAA	CCA	ATG	GTG	TAA	TCA	AAA	ACT	TAC	TAA	ATA	AAT	ATC	TAC	TAG	ACT	GTC	CTA	ACC	TTC
HTLV-II MOT		---	---	---	-A-	-G-	---	---	---	---	---	---	-T-	---	---	-C-	---	---	---	---	-T-	---	T--	---	---
HTLV-II NRA		---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
HTLV-II 30730		---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
HTLV-I ATK		-A-	-T-	-A-	-AC	-CT	-T-	---	-CA	-TC	-T-	---	C-C	--T	--T	---	-G-	-CT	-TA	CT-	--A	AA-	-CG	---	-A-
		CCC	TAG	ACA	ATG	CCA	TTC	ACA	AAG	CCC	TTT	GGA	CTC	TCA	ATC	AGC	TAA	ATG	TCA	TGA	ACC	CCA	GTG	GT	
HTLV-II MOT		---	---	---	---	---	---	---	---	---	---	---	-C-	---	---	---	---	---	---	---	---	---	---	---	---
HTLV-II NRA		---	---	---	---	---	-A-	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
HTLV-II 30730		---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
HTLV-I ATK		--A	-G-	-T-	---	-TC	-AT	C--	T--	---	-A-	---	-AA	---	-C-	-C-	--G	---	-GT	-A-	C-A	A-T	-CC	AC	

in PCR analyses for HIV-1 and HTLV-II DNA but not for HIV-2, HTLV-I, EBV, HHV-8, or HPV DNA. A Southern blot assay was negative for T-cell-receptor gene rearrangements, but the PCR assays for T-cell-receptor V_{β} and V_{γ} were both positive for clonal T-cell expansion; the V_{β} family 17 was the expanded clone. Quantitative PCR indicated that less than about 1 percent of the peripheral-blood mononuclear cells contained HTLV-II and V_{β} clonotype 17 DNA.

The cell culture of peripheral-blood mononuclear cells initially contained DNA for both HIV-1 and HTLV-II and produced HIV-1 p24 gag, HTLV-II p19 gag, p24 gag, and gp46 env proteins and reverse transcriptase activity. Initially, the V_{β} family 17 clone made up a minority of the cells. After several months of culture, however, HIV-1 DNA and protein disappeared from the culture, which remained positive for HTLV-II DNA and protein and produced typical type C retrovirus rather than particles that appeared to be HIV-1 on electron microscopy. The cell line remained dependent on exogenous interleukin-2. Phenotypic analyses at this time indicated that the cultured cells were CD3+CD8+CD4-CD45RO+CD25+CD20-. Southern blot analysis and PCR for T-cell receptor V_{β} were both strongly positive for clonal T-cell expansion, again of T-cell receptor V_{β} family 17. A Southern blot assay and PCR were both positive for HTLV-II DNA in approximately one copy of clonally integrated virus per cell as determined by banding patterns before and after restriction-endonuclease digestion.

Sequence analyses of the HTLV-II *pol* and *tax* DNA from the patient's skin, peripheral-blood mononuclear cells, and cultured T cells gave identical results. Phylogenetic analysis of these sequences indicated that they belonged to the HTLV-IIA subtype (Fig. 5 and data not shown).

DISCUSSION

HTLV-II is a member of a genus of oncogenic retroviruses. However, as compared with other members of this genus, including HTLV-I and the more distantly related bovine leukemia virus, HTLV-II infection seems to be associated with a much lower prevalence of virus-associated neoplasia.²⁸ When identified and characterized, however, the rare cancers

Figure 5. Alignment of 140 Bases of *pol* Gene Sequences from the Prototypic HTLV-IIA, HTLV-IIB, and HTLV-I Strains MOT, NRA, and ATK, Respectively, with Those of the HTLV-II Strain 30730 from the Patient with CD8+ Cutaneous T-Cell Lymphoma.

Amplified *pol* DNA from the patient's skin, peripheral-blood mononuclear cells, and CD8+ T-cell line was cloned. Eight different clones were sequenced in both forward and reverse directions. All sequences were identical. The HTLV-II 30730 sequences from the patient are identical to the HTLV-IIA prototype and are clearly distinct from HTLV-I; the dashes indicate conserved bases.

associated with HTLV-II have proved to involve CD8⁺ T lymphocytes, the predominant cell infected in the peripheral blood by HTLV-II. It would be reasonable to assume that in most asymptomatic patients with HTLV-II infection, the immune system plays a part in controlling the expansion of lymphocytes transformed by HTLV-II. Hence, it is possible that patients with HTLV-II infection who are also infected with HIV-1 may have a higher incidence of HTLV-II-associated T-cell leukemia-lymphoma over their lifetimes than patients with only HTLV-II infection.

In the United States, most cutaneous T-cell lymphomas, and virtually all of these that result from infection with HTLV-I, are of the CD3⁺CD4⁺CD8⁻ phenotype.²⁹ Rare cases of CD3⁺CD4⁻CD8⁺ cancers have been described.²⁹ To our knowledge, most of these cases of CD8⁺ cutaneous T-cell lymphoma have not been thoroughly evaluated for the presence of HTLV-I or HTLV-II. Other investigators have reported that many patients with classic CD4⁺ mycosis fungoides, with or without HIV infection, have been seronegative but have been positive on PCR for HTLV-I or HTLV-II.^{30,31} However, this has not been our own experience. Indeed, in a study of hundreds of T-cell lymphomas involving the skin, we have found only rare cases of HTLV seronegativity and PCR positivity (unpublished data).

Several cases of CD8⁺ T-cell lymphoproliferative disease have been described in patients with HIV-1 infection and have been associated with either HTLV-I or EBV.^{3,32,33} The condition of the patient we describe is very similar to that of two patients infected with both HIV-1 and HTLV-II who had severe erythrodermic desquamative skin disease.²⁰ The dermal infiltration in one of the patients was of CD3⁺CD8⁺CD4⁻ lymphocytes, but the cutaneous T-cell infiltrate was not subtyped in the other patient. No attempt was made to prove that the T-cell infiltrates were clonal and infected with HTLV-II.

In our patient, the data strongly suggest the presence of clonal, CD8⁺ T-lymphocytic, HTLV-II-associated neoplasia in the patient's skin and peripheral blood. The number of copies of both HTLV-II and V_β clonotype 17 DNA was much higher in the patient's skin than in the peripheral blood, a finding that further supports the hypothesis that HTLV-II was involved in the pathogenesis of the lymphoma. It is difficult to assess the natural history of this disease, given the fact that the patient died as a result of opportunistic infections secondary to his HIV-1-induced immunodeficiency, but he did derive clinical benefit from low-dose chemotherapy and therapy with total-body electron-beam irradiation. Further evaluations of populations in which HIV, HTLV-II, or both are endemic are clearly warranted to establish the incidence of CD8⁺ T-cell leukemia-lymphoma and to develop treatment strategies for these diseases, particularly now that combination antiretro-

roviral strategies have extended the life span of those infected with HIV.

Supported by grants from the Barbara Kopp Cancer Research Fund and the National Institutes of Health (HB 67021).

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