

Human T cell lymphotropic virus type I-associated infective dermatitis in Jamaica: a case report of clinical and biologic correlates

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Infective dermatitis was first characterized in Jamaican children as an exudative and crusting eczema (involving the nostrils, ears and scalp) with frequent relapse after treatment.^{1,2} In 1990 a case series of infective dermatitis from Jamaica provided the first link with early life infection with human T cell lymphotropic virus type I (HTLV-I).³ A subsequent case-control study confirmed this association and established criteria for diagnosis of HTLV-I-associated infective dermatitis.⁴ The diagnostic criteria include HTLV-I seropositivity; eczema of at least two of seven sites (scalp, external ear, retroauricular areas, eyelid margins, paranasal skin and/or neck, axillae, groin); chronic watery nasal discharge without other signs of rhinitis and/or crusting of the anterior nares; and either early childhood onset or chronic relapsing dermatitis.⁴ The prevalence of HTLV-I in the general population of Jamaica is 6.1%, and among women of reproductive age it is 3.8%.^{5,6} In Jamaica maternal-child transmission occurs at a rate of 18%, is primarily through breast-feeding and results in a HTLV-I prevalence of <2% among children younger than 10 years of age.^{5,6} Cases of infective dermatitis in HTLV-I-infected children have also been reported in Japan, Brazil, Colombia and Trinidad.⁷⁻¹⁰

Infective dermatitis is the earliest disease manifestation of HTLV-I infection in children, whereas adult T

cell leukemia/lymphoma and HTLV-I-associated myelopathy/tropical spastic paraparesis and HTLV-I-associated uveitis occur primarily among adults.¹¹ Linking these childhood and adult diseases are reports that patients with adult T cell leukemia/lymphoma and those with HTLV-I-associated myelopathy/tropical spastic paraparesis had been diagnosed with infective dermatitis 12 to 25 years earlier.^{7, 12, 13} Thus infective dermatitis in childhood may be a harbinger of HTLV-I-associated diseases in adult life.

In this report we describe an infective dermatitis case that arose among 28 HTLV-I-infected Jamaican children prospectively followed for up to 9 years to elucidate events leading to the onset of disease and to identify potential markers for persons at risk for HTLV-I-associated disease in adulthood.

METHODS

Study description. The subjects of this analysis were participants in the Jamaica Mother Infant Transmission Study.⁶ The protocol for this study was approved by Institutional Review Board committees at the National Cancer Institute and the University of the West Indies, Jamaica. Between January, 1989, and August, 1990, 212 HTLV-I-seropositive women who attended either of 2 antenatal clinics in Kingston, Jamaica, and their children were enrolled in the study. Mothers and children were followed in clinic every 6 weeks for the first 6 months, every 3 months up to 2 years of age and every 6 months thereafter. Peripheral blood samples along with information on physical examination, recent medical history and breast-feeding status were collected at each clinical visit. One of the 28 HTLV-I-positive children developed infective dermatitis during the study period.

HTLV-I. HTLV-I seropositivity was determined on sequential plasma samples by whole virus enzyme-linked immunoassay (Dupont, Wilmington, DE) and confirmed by a Western blot assay (Biotech, Rockville, MD). HTLV-I was distinguished from HTLV-II by Western blot. HTLV-I antibody titers were assayed by the endpoint dilution method using an enzyme-linked

Accepted for publication March 15, 2000.

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Key words: Human T cell lymphotropic virus type I, pediatric, infective dermatitis, Jamaica.

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immunoassay (Genetic Systems, Seattle, WA, or Cambridge-Biotech, Rockville, MD) at 4-fold dilutions.

Quantitative proviral DNA was measured by a real time automated PCR method. DNA was prepared from 1×10^6 viably frozen peripheral blood mononuclear cells (PBMC) using the PureGene DNA Isolation Kit (Gentra Systems, Inc., Minneapolis, MN). For each test sample, 10 μ l of DNA (300 μ g) was amplified for 45 cycles with AmpliTaq Gold polymerase using an ABI PRISM Sequence Detection System and TaqMan PCR Reagent (P/N N808-0230; PE Applied Biosystems, Foster City, CA) in a 98-well format.¹⁴ HTLV-I proviral load was normalized for the number of lymphocytes in each sample by dividing the number of provirus copies by the ratio of human endogenous retrovirus to gender code: 3 for male and 2 for female. This assay detects as few as 3 viral copies per 10^5 PBMC. The time of infection was estimated as occurring midpoint between the last sample with a negative signal and the first sample with a positive signal.

Flow cytometry. After peripheral blood samples were drawn into preservative-free heparin, mononuclear cells were separated by Ficoll-Hypaque density gradient centrifugation and washed, and aliquots of 5×10^6 cells were cryopreserved by controlled rate freezing. The samples were stored in liquid nitrogen until used for flow cytometry analysis. The cryopreserved lymphocytes were thawed, washed and incubated with 2% pooled human AB serum to block Fc receptors. The cells were resuspended in Dulbecco's phosphate-buffered saline plus 2% bovine serum albumin and labeled with conjugated monoclonal antibodies in a three color assay. A phycoerythrin/Cy-5 tandem anti-CD3 (CD3 Quantum Red, Sigma Chemical Co., St. Louis, MO) was used in each tube for quality control purposes and for gating of T cells. Other conjugated antibodies included IgG1, IgG2a, CD4, CD8, HLA-DR, CD25, CD45 and CD14 (Becton-Dickinson Immunocytometry Systems, San Jose, CA). A CD45/CD14/CD3 gating control was used to determine the optimum lymphocyte gating map. The negative control included IgG1/IgG2a/CD3. Samples were analyzed on a Coulter XL flow cytometer (Coulter Corp., Miami, FL).

Immunoglobulins. Quantitative immunoglobulin concentrations in serum were determined for IgG, IgA and IgM based on measurement of light scatter formation by nephelometry from an immunoprecipitation reaction (Beckman Array 360 analyzer; Beckman Company, Brea, CA). Quantitative IgE was determined using the Microparticle Enzyme Immunoassay (Abbott Imx; Abbott Laboratory, Abbott Park, IL).

Human leukocyte antigen (HLA) typing. DNA was extracted from PBMC by phenol-chloroform extraction. HLA Class I molecular typing was done using the PCR sequence-specific primers, in which well-

established primer pairs were used to amplify alleles.¹⁵ HLA Class II molecular typing was done by single strand conformation polymorphism analysis in combination with PCR sequence-specific primers.¹⁶

Statistical Methods. The incidence rate of infective dermatitis was calculated as the incidence density among 181 children born to HTLV-I-seropositive mothers, as well as among 28 of these 181 children who themselves were infected with HTLV-I. Person years (PY) were measured from date of birth to either development of infective dermatitis, date of death or last date of follow-up, whichever came first. Exact 95% confidence intervals (CI) for the incidence rates were calculated using confidence limit factors for estimating Poisson distributed variables.¹⁷ The probability of developing infective dermatitis by age 4 years was based on the cumulative incidence (incidence density \times 4).¹⁸

CASE REPORT

A 46-month-old boy was referred to the dermatology clinic for pruritic rash. The patient, a native of Kingston, Jamaica, had been well until 3 weeks earlier, when a fine papular, pruritic rash and sores on the scalp developed, along with swelling and discharge from the ears, redness in the right eye and occasional pruritus of the genitalia. These symptoms were treated with emulsifying ointment, tetracycline eye ointment and topical tetracycline to the ear, and oral antibiotics without significant improvement.

Notable medical history included recurrent episodes of multiple lymph node swelling at 3 and 4.5 months and two episodes of eye and ear infections without rash at 18 and 30 months of age, which resolved in 1 week with topical tetracycline. He also had a history of hepatomegaly at 21 months as well as eczema, swelling of multiple lymph nodes and hyperreflexia in both upper and lower extremities at 30 months of age. At 30 and 36 months, the child had hypochromic microcytic anemia (hemoglobin 8.4 g/dl), which was treated with oral iron supplements. The leukocyte count and differential were normal at that time. Other medical history was unremarkable, including history of allergy to drugs, contact dermatitis and various infectious diseases. Family history was also unremarkable, except for a history of allergic rhinitis in his 14-year-old sister. He had been breast-fed until 23 months of age.

At examination the patient was alert and afebrile with normal growth and vital signs. His skin showed crusting of the scalp, nose and retroauricular area. The retroauricular area was oozing and the ears were swollen. A fine papular rash extended from the face down to the upper trunk, where erythematous papules were present. Hyperpigmented papules were present in axillae. There was also scaliness and cracks around the base of the penis. Clinical diagnosis of infective dermatitis with otitis media was made. Laboratory

workup was unremarkable except for mild anemia (hemoglobin, 10.3 g/dl).

The skin lesions were treated with topical hydrocortisone and polysporin in addition to oral administration of trimethoprim-sulfamethoxazole and diphenhydramine hydrochloride. Approximately 6 months later fine papules remained on the face and trunk, albeit without crusting. The genital area was normal. Nine months after diagnosis mild conjunctivitis was present, but the skin condition was stable. The symptoms flared up with a few scattered papules and hypopigmented macules on the face, swollen eyelids with oozing and crusting around the nose at approximately 15 and 17 months after diagnosis when the patient was not receiving medication. At age 6 years the patient continued to have swelling of multiple lymph nodes, with 2.2% circulating abnormal lymphocytes. Between ages 6 and 7, he demonstrated intermittent hyperreflexia of upper and lower limbs with normal tone and without leg pain or weakness.

On his most recent clinical visit at age 7 years, the patient presented with mild scaling on the scalp, mild excoriation in the right ear, scattered skin colored papules on the face and upper chest and complained of mild itchiness of the legs. With continued medication (topical emulsifying ointment, mild topical steroids, topical and oral antibiotics and oral antihistamine), the child's condition remains stable.

RESULTS

We estimate that HTLV-I infection of this patient occurred at 27 months of age. HTLV-I proviral load measured 3000 copies per 10^5 cells at time of infection and increased linearly to 48 235 copies at 72 months of age, ~4 years after infection (Fig. 1). HTLV-I antibody titer peaked at time of infection (1:7000), followed by a precipitous decline 6 months later and a subsequent rebound to an intermediate level 1:4800 at age 72 months.

Analysis of T cell subsets was based on three samples obtained at 12 months (before infection), 36 months (midpoint between HTLV-I infection and disease onset) and 72 months (after disease onset). The CD4:CD8 ratio was 0.92 before infection, which 9

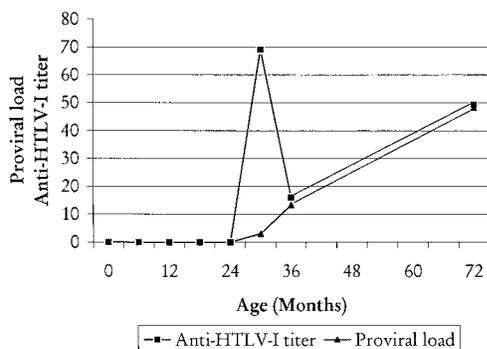


FIG. 1. HTLV-I viral markers by age (in months). HTLV-I proviral load is shown in thousands of copies per 100 000 cells; anti-HTLV-I titer is shown in hundreds.

months after infection increased to 1.78. This change reflected a 4-fold increase in percentage of $CD4^+CD25^+$ T cells (Fig. 2). Subsequent to diagnosis the CD4:CD8 ratio fell to 1.08, and the percentage of $CD4^+CD25^+$ T cells remained elevated at 3-fold higher than baseline.

Immunoglobulins (IgG, IgA, IgM, IgE) were measured on serial specimens that included five time points preceding infection (from 7 to 24 months), 3 time points between infection and diagnosis (from 30 to 42 months) and 2 time points postdiagnosis (78 and 84 months). Subtle abnormalities were detected for IgG, IgM and IgE. IgG was slightly above normal in the first measure after diagnosis (18.9 IU/ml; normal, 6.5 to 16.0) and returned to normal range 6 months later. IgM was low (386 IU/ml; normal, 450 to 2000 IU/ml) 1 month before onset of symptoms. IgE was increased 3 months preceding infection (184 IU/ml; normal, 2.0 to 149), but subsequent IgE measures were within normal range.

Because HLA types have been associated with risk of HTLV-I diseases, HLA DNA typing was performed to determine Class I and Class II alleles for this patient. Class I haplotypes were A*2 B*35 Cw*0401 and A*7401 B*8201 Cw*0302. Class II haplotypes were DRB1*1101 DQB1*0602 and DRB1*0302-DQB1*0402.

Our patient represents the sole case of infective dermatitis to develop in a cohort of 28 HTLV-I-infected and 153 uninfected children of HTLV-I-seropositive women. The median follow-up of the 28 infected children was 7.5 years (range, 1.4 to 9.0 years), accumulating a total of 180.9 PY of observation. The median follow-up of all 181 infected and uninfected children born to HTLV-I-seropositive women was 6.3 years (range, 0.8 to 9.1 years) totaling 906.3 PY of observation. The incidence rate of infective dermatitis among HTLV-I-infected children was 552 per 10^5 PY (95% CI 14 to 3080) (Table 1). The incidence rate among all 181 children of HTLV-I-infected women was 110 per 10^5 PY (95% CI 3 to 614). The probability of developing infective dermatitis by 4 years of age was 2.0% among the 28 perinatally infected children and 0.4% among the 181 children of HTLV-I-seropositive mothers.

DISCUSSION

Our patient met the major diagnostic criteria for HTLV-I-associated infective dermatitis based on HTLV-I seropositivity, onset of disease in early childhood, eczema with crusting of the scalp and retroauricular area, crusting of the anterior nares, as well as relapsing and remitting clinical course on withdrawal and resumption of therapy. Evidence consistent with minor diagnostic criteria included a generalized fine papular rash and anemia.⁴ Standard therapeutic treatment was provided and will probably be required until puberty, when severity of bacterial infections is expected to decrease.¹⁹

The most dramatic finding in this case was the high

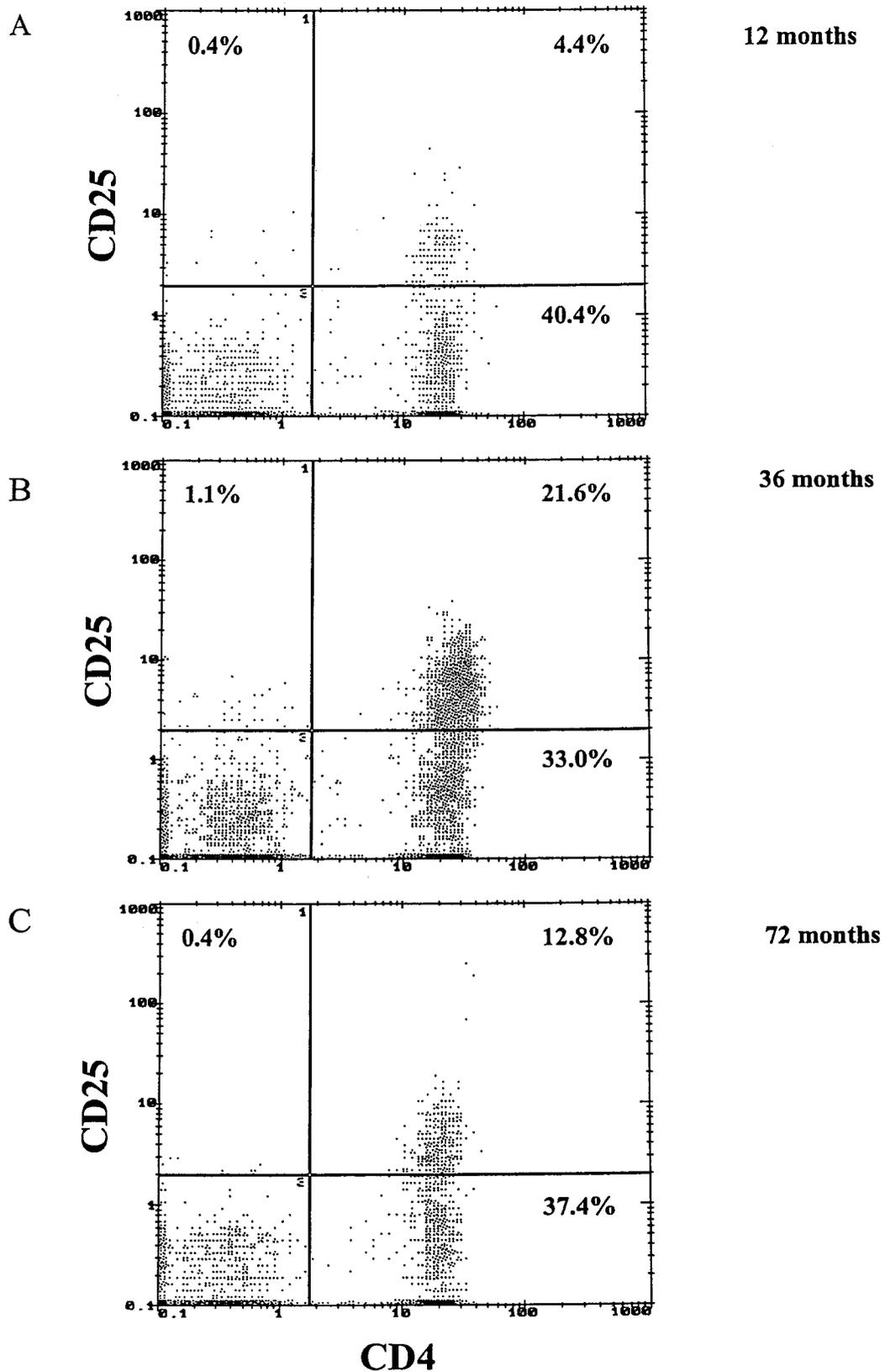


FIG. 2. Three color flow cytometric analysis of cryopreserved mononuclear cells stained with antibodies to CD3, CD4 and CD25. Lymphocytes were gated based on CD3 expression. The CD4 and CD25 expression of CD3⁺ lymphocytes is shown with T cells positive for both CD4 and CD25 appearing in the upper right quadrant. The percentage of gated cells positive for each antibody alone or coexpressing both CD25 and CD4 are shown in each panel. A, preinfection specimen obtained at 12 months of age; B, specimen obtained at 36 months of age, which was 9 months subsequent to infection; C, specimen obtained at 72 months of age.

TABLE 1. Incidence of infective dermatitis among HTLV-I-infected children and children born to HTLV-I-seropositive mothers in Jamaica

Subcohort	No. of Children	Total PY	Incidence per 10 ⁵ PY	95% CI
HTLV-I-infected children	28	180.9	552	14-3080
Children born to HTLV-I-seropositive mothers	181	906.3	110	3-614

HTLV-I proviral load (3000 copies/10⁵ cells) at time of infection and a marked linear increase with time. Among the other 27 HTLV-I-infected children, only one child had a proviral load similar in magnitude and that child had been diagnosed with dermatitis. High proviral load was predictive of the presence of abnormal lymphocytes in asymptomatic HTLV-I carriers²⁰ and has also been associated with HTLV-I-associated myelopathy/tropical spastic paraparesis,^{14, 21, 22} adult T cell leukemia/lymphoma²³ and HTLV-I-associated uveitis.²⁴ The observed high proviral load in the infective dermatitis patient indicates that this marker may also be predictive of infective dermatitis in the setting of perinatally acquired infection.

Our patient had an elevated CD4:CD8 ratio and an increased CD4⁺CD25⁺ T cell percentage 9 months after infection. Among HTLV-I-asymptomatic carriers, increased CD4:CD8 ratio and CD25⁺ T cells were associated with the presence of abnormal lymphocytes²⁵ that resemble malignant cells of adult T cell leukemia/lymphoma and likely reflect clonal expansion of HTLV-I-infected cells.²⁶ Two years after diagnosis our patient's CD4:CD8 ratio and CD4⁺CD25⁺ T cell percentage remained elevated, and abnormal lymphocytes were present. High levels of CD4:CD8 ratio and CD4⁺CD25⁺ T cells, along with the presence of abnormal cells, are characteristic of both adult T cell leukemia/lymphoma and HTLV-I-associated myelopathy/tropical spastic paraparesis.^{27, 28} Moreover similar hematologic changes, in addition to polyclonal integration of HTLV-I provirus, have been described as an intermediate state between carriers with clinical signs of immunodeficiency and both adult T cell leukemia/lymphoma and HTLV-I-associated myelopathy/tropical spastic paraparesis.^{27, 28} Although evaluation of clonality in this patient would help further to characterize this disease, reports of subsequent development of adult T cell leukemia/lymphoma and HTLV-I-associated myelopathy/tropical spastic paraparesis in patients with infective dermatitis,^{7, 12, 13, 29} together with the current observations, support the contention that infective dermatitis may be an early indicator of risk for HTLV-I-associated diseases in adults.

The proposed link between infective dermatitis and adult onset HTLV-I-associated diseases was further supported by the presence of HLA alleles Cw*04, DQB1*0602 and DRB1*1101 in our patient. Class I Cw*04 has been associated with a higher risk of

HTLV-I seroconversion after transfusion with HTLV-I-seropositive blood.³⁰ Class II allele DQB1*0602 has also been associated with HTLV-I infection and the diagnosis of adult T cell leukemia/lymphoma in patients from Japan and Jamaica.^{31, 32} In addition the frequency of Class II allele DRB1*1101, which has been previously reported in association with infective dermatitis, was also elevated among patients with HTLV-I-associated myelopathy/tropical spastic paraparesis or adult T cell leukemia/lymphoma.^{28, 32} These observations point to the similarities of genetic background between patients with infective dermatitis and those with adult T cell leukemia/lymphoma or HTLV-I-associated myelopathy/tropical spastic paraparesis and suggest that proposed susceptibility to these diseases in infective dermatitis patients could in part be explained by an immunogenic predisposition for these diseases marked by HLA haplotypes.

Prospective follow-up of children infected with HTLV-I allowed us to calculate the incidence rate of infective dermatitis. Our single case yielded an incidence rate of 522 per 10⁵ PY, which is considerably higher than that for adult T cell leukemia/lymphoma or HTLV-I-associated myelopathy/tropical spastic paraparesis among HTLV-I-seropositive adults in Jamaica (16 per 10⁵ and 22 per 10⁵, respectively).^{33, 34} Incidence rates for infective dermatitis in other countries where infective dermatitis has been reported have not been published. However, Trinidad's rates of adult T cell leukemia/lymphoma and HTLV-I-associated myelopathy/tropical spastic paraparesis are similar to Jamaica, whereas Japan has similar rates of adult T cell leukemia/lymphoma but lower rates of HTLV-I-associated myelopathy/tropical spastic paraparesis (0.4/100 000).³⁴⁻³⁷ Incidence rates for HTLV-I-associated diseases in Colombia and Brazil have not been reported, however, the prevalence of HTLV-I-associated myelopathy/tropical spastic paraparesis is known to be high (100/100 000 population) in Tumaco, Colombia.³⁸

Despite our efforts 7 of the 28 HTLV-I infected children completed less than 6 years of follow-up. Thus selective loss to follow-up of children who later may or may not have developed infective dermatitis could have underestimated or overestimated the incidence rate. A larger prospective study of HTLV-I-infected children is desirable to validate our observation. Such a study would also yield further information on the natural

course of HTLV-I pathogenesis in individuals highly predisposed to HTLV-I-associated diseases.

ACKNOWLEDGMENTS

We thank Dr. William Blattner of the Institute of Human Virology, University of Maryland, Baltimore, MD, for supervision of the research group in the design of the study; Ms. Beverley Cranston of the University of the West Indies, Kingston Jamaica, Ms. Jacqueline Murphy and Ms. Sylvia Cohn of Research Triangle Institute, Washington, DC, for study management and support; Dr. David Waters and Mr. Wendell Miley of Science Applications International Corp., Frederick, MD, for HTLV-I testing; Dr. William C. Kopp of Science Applications International Corp., Frederick, MD, for flow cytometric analysis; Dr. Yan-Yun Wu of the Clinical Pathology Department, Clinical Center, National Institutes of Health for immunoglobulin analysis; to Dr. Maureen P. Martin, Frederick Cancer Research Facility, National Cancer Institute, National Institutes of Health for HLA analysis.

This study was supported by funding of National Cancer Institute Research Contract N01-CP-40548.

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