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Human T-Cell Lymphotropic Virus Type I and Adult T-Cell Leukemia/Lymphoma Outside Japan and the Caribbean Basin

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Ninety-six patients with the diagnosis of adult T-cell leukemia/lymphoma (ATLL) were identified in countries outside Japan and the Caribbean Basin. Seventy-four of these patients were initially diagnosed in the United States; 25 of 52 patients whose places of birth were known had been born in the United States. The detection of 14 patients born in the southeastern United States, all black, indicates a group deserving particular attention for studies of human T-cell lymphotropic virus type I (HTLV-I), a suspected etiologic agent in most cases of ATLL. Although geographic clustering of ATLL in areas endemic for HTLV-I, particularly southwest Japan and the Caribbean Basin, is a dramatic feature of this disease, a review of the literature indicates that HTLV-I–associated ATLL probably occurs sporadically in a much wider distribution, the disease being diagnosed in native-born African, Chinese, European, and Latin American patients. A registry for ATLL cases is suggested, to assist in the identification of risk factors for this disease and, at the same time, improve case definitions and early diagnosis.

INTRODUCTION

Adult T-cell leukemia/lymphoma (ATLL), a hematologic malignancy associated with the first isolated human retrovirus, human T-cell lymphotropic virus type I (HTLV-I), is an aggressive malignancy most frequently found in southwest Japan, particularly in the Goto Islands where the estimated incidence rate is 24.2/100,000 [1], and also on certain Caribbean islands such as Jamaica, where approximately half of the non-Hodgkin's lymphoma cases are ATLL [2]. The geographic clustering of HTLV-I and ATLL in the same restricted areas is particularly striking and supports the etiologic relationship between the virus and the malignancy [1,3].

HTLV-I is extremely cell-associated and, therefore, is not readily transmitted. Current evidence suggests at least four likely routes of transmission for this virus. Transmission from mother to child has been well documented [4–6]. Infection in utero and peripartum are both possible, but the demonstration of HTLV-I in breast milk and data from observational studies in Japan suggest that breast feeding is the major mother-child transmission mechanism. The concern about transmission via breast milk has led Japanese workers to advise HTLV-I–seropositive mothers not to nurse their children [7], but this suggestion would not be practical in poorer countries, where

Abbreviations: ATLL: adult T-cell leukemia/lymphoma EBV: Epstein-Barr virus HLA: human leukocyte antigen HTLV-I: human T-cell lymphotropic virus type I

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TABLE 1
Diagnostic Criteria for Adult T-Cell Leukemia/Lymphoma (ATLL)

1. Malignant mature T-cells
2. Peripheral blood involvement
3. Polylobulated lymphocytes
4. Skin manifestations
5. Hypercalcemia/bone lesions
6. Lymphadenopathy/hepatosplenomegaly

infants would clearly be at higher risk of death from malnutrition if they were not breast-fed. Transfusion of HTLV-I–positive blood is another apparent route of infection [8,9]. Epidemiologic studies have suggested that transfusion of HTLV-I–infected blood may be responsible for the subsequent development of HTLV-I–associated myelopathy or tropical spastic paraparesis [10], another disease suggested as being due to HTLV-I [11–14]. There have been no reports, however, of ATLL linked to transfusion. Regarding other routes of transmission, there is considerable evidence for transmission of HTLV-I by sexual activity, particularly from male to female [15], and via needle sharing among intravenous drug abusers [16]. The implications of these findings are quite important in view of the great potential for males to transmit HTLV-I to their female sexual partners, who could then readily pass the virus to their offspring. Mosquitoes are unlikely to be vectors for HTLV-I infection, as shown by both laboratory [Reeves W: personal communication] and epidemiologic [1,3] studies.

While ATLL has been reported most often in people of Japanese and African descent, this disease has a wide geographic distribution and occurs in people of virtually all racial/ethnic groups. The precise delineation of the pattern of ATLL, however, is obscured by several factors. First, ATLL is not a homogeneous histopathologic entity [17–19], a spectrum of histologic subtypes being found both in endemic [2,19] and non-endemic [17,20] regions. As of this date, no particular histologic subtype has been shown to correlate with any particular clinical or demographic feature of ATLL. When there is skin involvement, the differentiation between ATLL and mycosis fungoides can be particularly difficult, even for hematopathologists possessing considerable experience with these diseases. Therefore, the diagnosis of ATLL rests on a constellation of clinical and pathologic features (Table 1). The most consistent pathologic feature is the presence of circulating polylobulated lymphoid cells. While the presence of malignant mature T cells is a hallmark of the disease, this criterion cannot always be documented, since not all hospitals routinely type tumors from patients with hematologic malignancies. The prominence of the other signs in various series will be discussed later.

A second controversial area is the role of HTLV-I assays in the diagnosis of ATLL. The presence of HTLV-I antibody in a patient with clinical signs and symptoms of ATLL is *suggestive* but not conclusive, since many individuals, both cancer patients and those with no apparent disease, can have antibodies to HTLV-I totally unrelated to any pathogenic process; however, the finding of HTLV-I provirus integrated into the tumor cells of a patient with the clinical features listed here makes the diagnosis of ATLL unequivocal. One problem faced by investigators studying ATLL is that there is no complete agreement as to how to classify HTLV-I–negative patients. Currently,

since seronegative patients have been identified in Japan [19] and Jamaica [2] with clinicopathologic features indistinguishable from seropositive ATLL, most investigators do not require evidence of HTLV-I infection in making the diagnosis of ATLL. This issue will need to be re-evaluated as more cases are collected and more laboratory assays are applied to disease classification.

At the National Cancer Institute, we have begun to collect cases diagnosed as ATLL from areas outside Japan and the Caribbean in order to improve the case definition as well as to address the following questions:

1. Can we identify any particular risk factors, other than HTLV-I, consistently distinguishing ATLL cases from the general population?

2. Will our identification of ATLL cases lead to finding "clusters" of HTLV-I infection that have not previously been recognized?

3. Are there any features that distinguish HTLV-I–positive ATLL (defined by viral genome detection rather than antibody positivity) from HTLV-I–negative cases?

4. Can we define any serologic profiles useful in predicting disease outcome comparable to the use of Epstein-Barr virus (EBV) serology in Burkitt's lymphoma and nasopharyngeal carcinoma?

5. By reviewing the clinical histories of U.S. cases, can we develop mechanisms to alert clinicians to early detection and more effective treatment of this disease?

MATERIALS AND METHODS

The source of cases for this series included patients whose sera have been sent to our laboratory for HTLV-I antibody testing (37 cases), cases referred to one of us (EJ) for pathologic confirmation (22 cases), patients that our group has personally investigated (12 cases), and cases gleaned from the literature (three U.S. patients and all non-U.S. patients).

RESULTS

ATLL cases diagnosed in the United States had many characteristics of cases identified in the Caribbean Basin (Table 2); the median age was 55.5 years for males and 50.5 years for females, most patients were black, and the disease usually pursued an aggressive course. Males predominated in the U.S.-born cases (16 males, 9 females) but not in those born outside the U.S. (11 males, 16 females).

Information available thus far regarding place of birth (Table 3) confirms the suggestion by Blayney et al. [21] that the southeastern U.S. is an important focus of ATLL, with 14 of the 25 native U.S. cases being born in the Carolinas, Georgia, Alabama, and Florida. Of these 14 patients, all were black. The identification of a significant proportion of cases born in the Caribbean region and Japan is not surprising, since it is well known that being born in an ATLL-endemic area is a major risk factor for the disease. Furthermore, the development of ATLL in patients born in Latin America is consistent with our concurrent studies in Panama and Colombia, where there are several reported cases of ATLL in native-born Latin Americans [20,22].

The prognosis of ATLL is generally unfavorable regardless of the type of therapy employed. In our series, the median survival time was two months. One patient with an exceptionally long remission, a woman born in Tokyo, was first diagnosed with ATLL

TABLE 2
Demographic Features of ATLL Patients Diagnosed in the U.S.[a]

	Male	Female
	U.S.–Born Cases	
Sex	16	9
Age		
Median (range)	55.5 (26–76)	50.5 (26–71)
Racial/Ethnic Origin		
Black	12	8
White	3	0
Hispanic/Mestizo	0	0
Japanese	1	1
	Non-U.S.–Born Cases	
Sex	11	16
Age		
Median (range)	43 (30–58)	44 (23-66)
Racial/Ethnic Origin		
Black	7	11
White	2	0
Hispanic/Mestizo	2	3
Japanese	0	2

[a]Place of birth not identified in 22 patients

TABLE 3
Place of Birth of 74 ATLL Cases Diagnosed in the United States

Cases	Place of Birth	No. of Cases
U.S.-born (25)[a]	South Carolina	6
	Alabama	2
	Florida	2
	Georgia	2
	Hawaii	2
	New York	2
	North Carolina	2
	Tennessee	2
	Alaska	1
	District of Columbia	1
	Louisiana	1
	Massachusetts	1
	Texas	1
Foreign-born (27)	Jamaica	8
	Haiti	4
	Colombia	2
	Japan	2
	Trinidad and Tobago	2
	Brazil	1
	Chile	1
	Curacao	1
	Dominican Republic	1
	Ecuador	1
	Grenada	1
	Honduras	1
	Israel	1
	St. Lucia	1

[a]Place of birth not identified in 22 patients

TABLE 4
Clinical Features of ATLL

	Overall [18] No. (%)	Japan [19] No. (%)	Jamaica [32] No. (%)	U.S.A. and Panama [18,20] No. (%)
Clinical				
Leukemia	159/263(60)	115/197(58)	25/42(60)	19/24(79)
Hypercalcemia	97/255(38)	57/192(30)	23/42(55)	17/21(81)
Bone marrow infiltration	129/259(50)	104/197(53)	19/42(45)	6/20(30)
Generalized lymphadenopathy	173/261(66)	117/197(59)	39/42(93)	17/22(77)
Skin involvement	89/263(34)	67/197(34)	10/42(24)	12/24(50)
Hepatosplenomegaly	84/261(32)	56/197(28)	16/42(38)	12/22(55)
Lytic bone lesions	4/24(17)	0/4(0)	N.R.	4/20(20)

N.R.: not reported

in 1983 at the age of 40, and after chemotherapy with six months of cyclophosphamide, adriamycin, methotrexate, vincristine, VP-16, and prednisone, she achieved a remission which persisted for four years until disseminated disease appeared in December 1987.

The clinical features of the patients in our U.S. series, comparable to the data reported by Clark et al. [18], are generally similar to those in other geographic locales. While we find an increased incidence of hypercalcemia and lytic bone lesions in the U.S. over that reported in Japan and the Caribbean (Table 4), this finding may be due to an emphasis on these features in our early case reports [23], since a lower frequency of hypercalcemia has been observed in our more recent patients.

Serologic studies for HTLV-I were performed in 69 of our 74 patients; 68 of these sera were reported to be antibody-positive by a screening ELISA test, but confirmation by our more specific assays was performed on only 44 of these sera. Virologic studies were performed on cell cultures derived from the malignant T lymphocytes of seven of these patients, all demonstrating the presence of HTLV-I genome in the tumor cells.

We have thus far identified 22 cases of ATLL diagnosed outside Japan, the Caribbean islands, and the United States [20,22,24–29]. While 11 were born in the Caribbean Basin [24,25], other reports indicate that ATLL can occur in lifetime residents of Africa [27], Asia [28,29], Europe [26], and Latin America [20,22]. Serologic and virologic studies in some of the patients born outside Japan and the Caribbean islands have included documentation of HTLV-I viral genome in the tumor cells [26,27] or cell lines derived from tumor cells [24], one patient with viral genome-positive tumor cells having no HTLV-I antibody detectable in the serum [26].

DISCUSSION

ATLL was first identified as a clinical-pathologic entity in 1977 by Uchiyama et al. [30], who observed a series of cases with the classical features of leukemia, hypercalcemia, lymphadenopathy, and skin lesions in Tokyo. The subsequent association of HTLV-I with classical cases in the endemic areas of Japan and the broadening spectrum of clinical manifestations accepted as part of ATLL have blurred the definition of this disease and have led to difficulties in the development of epidemiologic studies, particularly in areas where both case identification and detection of antibodies to HTLV-I are infrequent.

In an attempt to clarify the epidemiology of ATLL, we have thus far identified 74 cases diagnosed as ATLL in the U.S. and 22 cases diagnosed in other countries outside Japan and the Caribbean Basin. Because information on patients not seen at the NIH is incomplete, and the registration is not population-based, our results may be biased. Nevertheless, several features of importance have emerged, identifying areas for future research.

The large percentage of patients born in the southeastern United States provides additional support to the observation of Blayney et al. [21] that this area deserves further study in regard to the distribution of HTLV-I, particularly in the black population. Two other interesting findings in this series of patients are the higher frequency of hypercalcemia in comparison to series from Japan and the Caribbean and the important, although unusual, observation that aggressive chemotherapy can lead to prolonged unmaintained remission of greater than four years. Regarding the hypercalcemia, this finding could represent reporting bias, possibly due in part to the emphasis on hypercalcemia in previous clinical reports [18,23].

In regard to the identification of risk factors other than HTLV-I, additional cases are needed before the leads generated by studies in Japan and the Caribbean Basin are pursued. Lower socioeconomic status has been reported to be important in Japan and the Caribbean but has not been rigorously examined in the U.S. Certainly infection with HTLV-I and being born in an area with a higher incidence of ATLL appear to be significant risk factors in the U.S. Finally, the role of genetics in the etiology of ATLL remains uncertain. The high prevalence in two genetically diverse groups such as Japanese and Caribbean blacks suggests a relatively unimportant role for genetic susceptibility, but it would be premature at this time to rule out completely genetic susceptibility as one contributing factor, particularly in view of a report by Usuku et al. suggesting an association between human leukocyte antigen (HLA) type and ATLL in Japan [31].

Further progress in studies on the etiology and control of ATLL will depend in large part on a more precise case definition of this disease. At the present time, only those cases with typical clinicopathologic features and HTLV-I provirus detected in the malignant tumor cells are accepted universally as being ATLL. Serologic identification of HTLV-I antibody is a useful screening test for this disease, but seropositive patients may not have virus integrated into the tumor cells and, conversely, viral integration can occur without detectable antibody. Evaluation of a broad base of malignant lymphoproliferative diseases is necessary to define the entire clinical spectrum of ATLL. In view of the need to clarify the definition of ATLL as well as its value as a sentinel to pockets of HTLV-I infection, the development of a registry of ATLL cases could be of great value.[1]

[1]Physicians are encouraged to report any suspected cases of ATLL to Dr. Levine at the National Cancer Institute (301-496-4375). Serologic and pathologic evaluations will be performed at NIH expense.

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