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Adult T-cell leukemia/lymphoma in HTLV-1 non-endemic regions

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ABSTRACT

Background: HTLV-1 infection is a neglected disease, despite producing neurological and lymphoproliferative severe illnesses and affect over 10 million people worldwide. Roughly 5% of HTLV-1 carriers develop Adult T-cell leukemia/lymphoma (ATLL), one of the most aggressive hematological malignancies.
Methods: A national HTLV-1 register exists since 1989 in Spain, a non-endemic country with a large migrant flow from Latin America and Equatorial Africa, where HTLV-1 is endemic. The main features of all patients diagnosed with ATLL in Spain up to date are reported.
Results: A total of 451 cases of HTLV-1 infection had been reported in Spain until the end of year 2022. ATLL had been diagnosed in 35 (7.8%). The current average incidence of ATLL in Spain is of two cases per year. Women represent 57% of ATLL patients. Mean age at diagnosis was 47 years-old. Roughly 57% were Latin Americans and 26% Africans. At diagnosis, the majority presented with acute or lymphoma clinical forms. Survival was shorter than one year in most of them.
Mean HTLV-1 proviral load was significantly greater in ATLL patients than in asymptomatic HTLV-1 carriers (2,305 vs 104 copies/10^4 PBMC). HTLV-1 subtyping in 6 ATLL patients found the 1a transcontinental variant ($n = 4$) and the Japanese variant ($n = 2$). All ATLL patients were negative for HIV-1, did not develop HTLV-1-associated myelopathy and were not transplant recipients.
Conclusion: The rate of ATLL is very low in Spain and mostly associated to migrants from HTLV-1 endemic regions. Given the poor clinical outcome of ATLL, HTLV-1 testing should be performed at least once in all migrants coming from HTLV-1 endemic countries and in natives who have lived in or had sex partners from such regions.

1. Introduction

Infection with HTLV-1 is a neglected condition, despite being the second most prevalent human retroviral infection worldwide after HIV-1 [1]. Current estimates are of 10 million people living with HTLV-1 globally, with high endemic regions located in Equatorial Africa, Latin America and the Caribbean, northeastern Iran, southwestern Japan and Australia [1–3]. Once acquired, either sexually, vertically or parenterally, HTLV-1 infection is lifelong. Although many HTLV-1-infected individuals are asymptomatic and unaware of their infection, roughly 10% will go to develop clinical manifestations. The time to onset of disease after HTLV-1 primary infection is generally very long (several decades) for adult T-cell leukemia/lymphoma (ATLL) whereas for HTLV-1-associate myelopathy (HAM) this time can be short is some cases, especially after blood transfusion or transplantation [4–6].

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In 1989 Shimoyama classified ATLL into four clinical forms [7]. Whereas the acute and lymphoma forms are considered aggressive diseases, the chronic and smoldering forms are viewed as indolent conditions. In any clinical form, cutaneous involvement is associated with poorer prognosis [8]. Progression to acute or lymphomatous forms occurs in a significant proportion of patients originally presenting with indolent forms [9,10].

Herein, we discuss the main features of patients diagnosed to date with ATLL in Spain, a country of 47 million people, with a large migrant flow from regions in Latin America and Equatorial Africa where HTLV-1 is endemic.

2. Methods

A nationwide HTLV-1 register was created in Spain in 1989. Main demographics, clinical symptoms/signs and laboratory findings are collected for each new HTLV-1 case at baseline and longitudinally using a standardized case report form (Supplementary Table 1). Members of the Spanish HTLV Network cover nationwide most of the lab facilities where this virus can be diagnosed, including public or private microbiology labs and blood banks [11].

Notification of HTLV-1 positives to the national register is voluntary. However, from the coordination team, clinics are contacted when new cases are identified at the public National Hospital Discharge database and there is no prior recording at the HTLV-1 register [12,13]. Ultimately, provision of free access to diagnostic tools including HTLV-1 proviral load and subtyping, facilitates and ensure that almost all HTLV-1 cases are recorded within 1–2 years upon first diagnosis in Spain.

Since HTLV screening is not routinely offered to the general population, most HTLV-1 diagnoses are reported by sites that run targeted screening in currently recommended populations, such as migrants coming from endemic regions in transplantation centers, blood banks and obstetric clinics. In addition, HTLV-1 positives are identified in health care sites where patients may present with suggestive clinical manifestations, mostly neurological or hematological syndromes. A third source of HTLV-1 cases in Spain result from periodic multicenter surveys carried out by the Spanish HTLV Network, testing pregnant women, foreigners and/or individuals with sexually transmitted infections. Finally, contact tracing of HTLV-1 positives provides an additional number of cases. In year 2022, a total of 22 new individuals with HTLV-1 were diagnosed in Spain. Six of them first presented with clinical manifestations, such as HAM ($n = 3$) or ATLL ($n = 2$). Sixteen were from Latin America and two from West Africa. One was from Iran. Only two were native Spaniards. During 2022, 8 new reported cases of HTLV-1 were blood donors. Universal HTLV screening of organ and stem cell donors became mandatory in Spain in 2019. Since then, no HTLV-1-positive organ donors have been identified.

Access to health care in Spain is easy, since all natives and migrants can be attended free of charge at public facilities when presenting with acute syndromes. With respect to non-acute medical appointments, either at private or public clinics, patients have to be insured. Otherwise, they are charged. Most migrants living in Spain are legal residents and benefit from free of charge medical attendance at the public health system. The situation is different for illegal migrants, but they represent a relatively low population.

The diagnosis of ATLL and its four major clinical forms was made following clinical, laboratory, and histological criteria originally reported by Shimoyama [7]. Briefly, individuals with a proliferation of clonal CD4+ T lymphocytes in lymph nodes and/or blood along with a reactive HTLV-1 serology were split out in either aggressive or indolent forms, each one with two modalities. In the acute type, leukemic cells were present in the blood besides lymph nodes and body organs. In the lymphomatous form, tumor cells are limited to adenopathies and extranodal sites, with no peripheral blood expression. In the chronic type, T lymphocytosis and elevated LDH up to twice the normal limit and without organ involvement are present. Finally, in the smoldering form more than 5% of abnormal T lymphocytes are circulating without overt lymphocytosis, lymphadenopathies or extranodal involvement.

2.1. Statistical analysis

Figures are given in absolute numbers and percentages. Quantitative and qualitative variables are described as medians with interquartile ranges, mean with standard deviations or as proportions. Bivariate comparisons of quantitative variables were performed using the Chi^2 test.

All statistical analyses were performed using the IBM SPSS package for Windows v25.0 (IBM Corp, Armonk, NY). All tests were two-tailed and only p values <0.05 were considered as significant.

2.2. Ethical approval

The study was designed as a multicentre and retrospective collection of anonymized and consecutive clinical data associated to serum HTLV-1 antibodies. It was approved by the International University of La Rioja (UNIR) ethics committee (ref. PI047/2023).

3. Results

The Spanish HTLV-1 network updates on a yearly basis the national figures for this viral infection and produces recommendations for screening and/or medical management. The 2022 annual meeting was held in Madrid on December 14th 2022. A total of 451 cases of HTLV-1 had been recorded in Spain until then. HAM had been diagnosed in 58 (12.9%) and ATLL in 35 (7.8%). The first case of ATLL in Spain was reported in 1985 in a native Spaniard old woman living in Barcelona who died soon after being diagnosed [14]. A second case was reported in 1989 in a Chilean migrant living in Barcelona [15].

Fig. 1 depicts graphically temporal trends in ATLL diagnoses reported in Spain over the last three decades. The current incidence of ATLL in Spain is on average of 2 new cases per year. It has remained quite stable within the last 15 years.

Women represented 57% of ATLL patients at the Spanish register (Table 1). Mean age at diagnosis was 47 years-old. Roughly 57% of ATLL patients in Spain were migrants from Latin America and 26% from Sub-Saharan Africa. However, native Spaniards represented 17% of ATLL patients. All but two for whom information was available, had lived in endemic regions for long periods and/or her mother was from such regions.

Most ATLL patients in our series presented with aggressive clinical forms, either acute ($n = 12$) or lymphoma ($n = 19$) types. Their survival was less than one year in most cases. None of ATLL patients in our series was coinfected with HIV-1 and none presented with symptoms/signs of HTLV-1 associated myelopathy. Furthermore, none was a transplant recipient. The only patient recorded in Table 1 as most likely infected by transfusion/transplantation, had received a blood transfusion two decades earlier for other reasons than transplantation.

The HTLV-1 proviral load could be tested in 91 patients, including 20 with ATLL, all with aggressive forms either leukemia or lymphoma. The mean HTLV-1 proviral load in ATLL patients was significantly greater than in asymptomatic HTLV-1 carriers (2305 vs 104 copies/10^4 peripheral blood mononuclear cells). Characterization of HTLV-1 subtyping was made in 108 patients. In 6 patients with ATLL, the HTLV-1 subtype 1a transcontinental variant was found in four and the Japanese variant in two.

4. Discussion

Global estimates for HTLV-1 infected individuals are of 10 million people, with hot spots distributed across all continents [2,3]. High rates of HTLV-1 infection have been reported among aboriginal people in

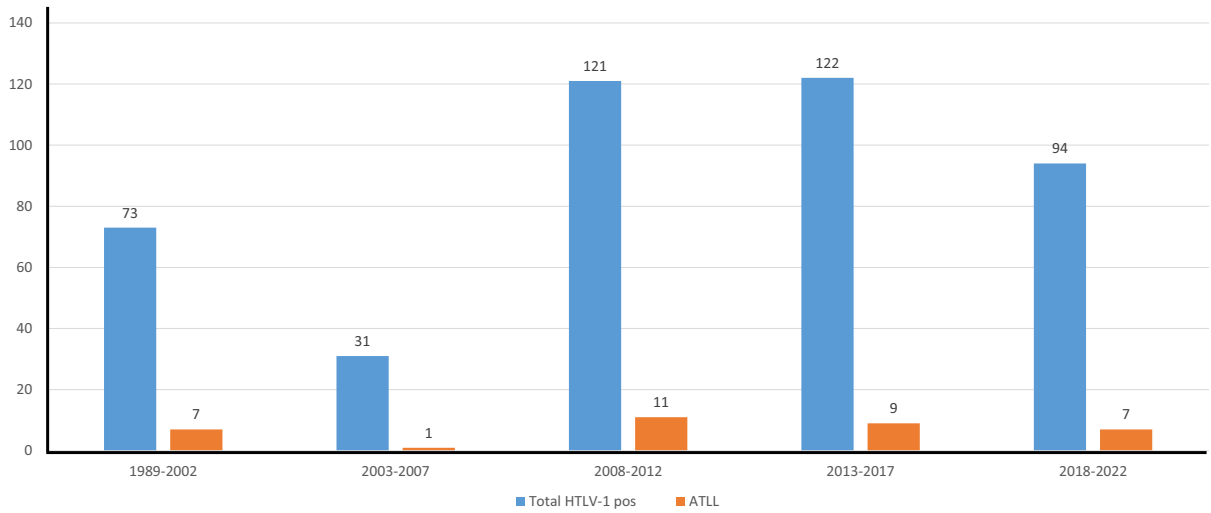

Fig. 1. Calender reporting of HTLV-1 and ATLL in Spain. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Main features of individuals with HTLV-1 infection and ATLL in Spain.

	All HTLV-1	No ATL	ATL	P
N (%)	**451**	**416**	**35**	**–**
Female sex	286 (63.4)	266 (63.9)	20 (57.1)	0.42
Mean age (years)	43	41	47	0.1
Region of birth (n,%)				
Latin America	298 (66)	278 (66.8)	20 (57.1)	0.24
Africa	52 (11.5)	43 (10.3)	9 (25.7)	0.006
Spain	74 (16.4)	68 (16.2)	6 (17.1)	0.9
Others	27 (6)	27 (6.5)	0	0.24
City of residence (n,%)				
Madrid	144 (31.9)	139 (33.4)	5 (14.3)	0.019
Barcelona	130 (28.9)	111 (26.7)	19 (54.3)	0.14
Canary islands	8 (1.8)	6 (1.4)	2 (5.7)	0.07
Others	169 (37.5)	160 (38.5)	9 (25.7)	0.19
Presumed transmission route (n,%)				
Sexual*	145 (32.1)*	140 (33.6)	5 (14.3)	0.018
Vertical	45 (10)	39 (9.4)	6 (17.1)	0.14
Transfusion/ Transplantation	17 (3.8)	16 (3.8)	1 (2.9)	0.76
Others or unknown	244	221	23	0.15
HIV-1 coinfection (n,%)	16 (3.5)	16 (3.8)	0	0.1
HTLV-1 subtype 1a (n,%)**	103	97	6	
Transcontinental variant	87	83	4	
Japanese variant	5	3	2	
Others or missing	5	4	1	
Median HTLV-1 proviral load (copies/104 PBMC) (IQR)***	259 (37–1428)	104 (10–804)	2305 (1596–6346)	0.001

* Heterosexual contacts in most cases (all but 7).
** HTLV-1 subtyping could be obtained on 108 patients.
*** Proviral load could be performed on 91 patients.

Australia, Equatorial Africa, Latin America and the Caribbean, northeastern Iran, and southwestern Japan [1–3]. HTLV-1 is an intracellular virus transmitted throughout body fluids, including blood, semen and milk. Accordingly, sexual exposure, breastfeeding, transfusions, needle sharing in drug users, etc. pose individuals at risk for contagion.

Children born from infected mothers may acquire HTLV-1 when breastfeeding extends beyond 3 months, since passively transmitted mother's antibodies at birth protects the baby until then [16]. Following implementation of HTLV-1 antenatal screening in Japan, new infections in adolescent and adult generations throughout sexual contact have replaced vertical transmission as the main route for transmission. Being Japan a country of 125 million population, a recent survey estimated that roughly 3000 new HTLV-1 infections occur annually [17]. A longitudinal assessment of ATLL rates in Japan has acknowledged a decline within the last decade, most likely reflecting the drop in perinatal infections after introducing universal pregnant screening [18].

Outside endemic regions, HTLV-1 infection is mostly diagnosed in migrants coming from countries with high HTLV-1 prevalence. Less frequently, HTLV-1 is found in natives that had lived in endemic countries or had sex partners from such regions. In our series of 35 patients diagnosed with ATLL, only 6 (17%) were native Spaniards. Of note, some had lived in endemic regions for long periods or his/her mother was from such regions.

ATLL is a malignancy of mature CD4 + T cells induced by HTLV-1. The virus maintains life-long infection in the human host by clonal proliferation of infected cells. Two viral genes, tax and HTLV-1 bZIP factor (HBZ), promote expansion of infected cells by producing acceleration of cell proliferation and protection from cell death [19,20]. Immune evasion is a critical step in the oncogenesis of ATL [21].

ATLL is classified into four clinical subtypes: acute, lymphoma, chronic, and smoldering [7]. Chronic ATLL is further divided into unfavorable and favorable chronic types according to serum lactate dehydrogenase, blood urea nitrogen, and serum albumin values. Acute, lymphoma, and unfavorable chronic types are categorized as aggressive ATLL, whereas favorable chronic and smoldering types are categorized as indolent ATLL [22]. Intensive chemotherapy alone is not sufficient to prevent relapse of aggressive ATLL. Allogeneic hematopoietic stem cell transplantation is a potential therapeutic option to cure aggressive ATLL in younger patients. Reduced-intensity conditioning regimens have decreased transplantation-related mortality, and increased donor availability has dramatically improved transplant access. New agents, including mogamulizumab, brentuximab, tucidinostat, and valemetostat, have recently become available for patients with aggressive ATLL [23]. In our series of 35 ATLL collected over three decades, the majority with aggressive acute or lymphoma forms, the survival was short in almost all cases. None of our ATLL patients received any of the drugs mentioned above. In a series of 143 ATLL patients from Bahia, Brazil, the longest survival was of 109 months for patients with the smoldering

type, whereas it was less than 50 months for the rest. The presence of cutaneous lesions predicted a worse outcome [24].

Roughly 5% of HTLV-1 carriers develop ATLL, in Japan generally after the sixth decade of life. A high proviral load in the blood predicts the development of ATLL. Compared to Japanese patients, ATLL in Caribbeans appears at younger age and female represent more than half of patients. The acute form of ATLL is the most frequent at diagnosis in Caribbeans and the prognosis is very poor, with an overall survival of only 11% at 4 years [25]. This profile instead of the Japanese is the one we most frequently recognized in our ATLL patients in Spain.

A concurrent diagnosis of ATLL and HAM is rare. There are anecdotal cases with rapid progression of subacute myelopathy accompanying acute or lymphoma clinical ATLL forms [26,27]. In our series, none of our 35 patients with ATLL developed HAM.

Given shared mechanisms of transmission, coinfection with HIV-1 can be recognized frequently in HTLV-1 carriers [28]. Indeed, 16 out of 451 cases (3.5%) in the Spanish register were coinfected with HIV-1 and HTLV-1 [29]. However, none of the 35 patients with ATLL had HIV-1 coinfection. We believed that this finding might indirectly support that most of our ATLL patients would have acquired HTLV-1 vertically via breastfeeding from her infected mothers rather than through sexual contact. In a single center study in the United States, none of 23 HTLV-1 cases identified over two decades had HIV-1 coinfection. Two thirds were of African ethnicity and eight patients presented with ATLL [30].

In a large series of kidney transplants from Japan, where HTLV-1 is endemic, a total of 180 individuals were HTLV-1 positive, either the donor, the recipient or both. Only one individual developed both HAM and ATLL on follow-up, after 8 and 10 years, respectively. He was HTLV-1 positive before kidney transplantation and the donor had been HTLV-1 negative [31]. In our series of 35 ATLL cases in Spain, none was a transplant recipient. In contrast, five cases out of 58 HAM cases that have been diagnosed in Spain up to date, were recipients of solid organ transplants from HTLV-1 positive donors [32–34].

We should acknowledge several limitations of our study. Firstly, given its retrospective design, some important clinical information could not be obtained for a subset of patients, especially those diagnosed with ATLL before year 2000. No further clinical information could be obtained for ATLL cases, since the HTLV-1 case report form only records epidemiological and demographics data rather than specifics on clinical information, including ATLL subtype variants. The register was originally not intended to establish a cohort followed longitudinally. Secondly, biological specimens needed for examining virological parameters, such as proviral load and/or HTLV-1 subtyping, were not available for all patients. Thirdly, the management of ATLL was not uniform and therapeutic strategies, including the use of distinct chemotherapy regimens, antiretrovirals, interferon, new monoclonal agents and the performance of hematopoietic stem cell transplantation were chosen by doctors in charge, without uniform criteria, at their respective centers. Furthermore, the clinical management changed over time.

Fourthly, HTLV-1 and ATLL underreporting must be presumed, as previously noticed in other non-endemic countries [35]. The awareness about HTLV-1 among Spanish clinicians specialized in hematology, neurology or dermatology is low on average. The number of patients diagnosed each year with leukemia/lymphoma in Spain is roughly of 6500 new cases of leukemia and 10,000 new cases of non-hodgkin lymphoma. Lymphocytic T-cell neoplasias represent only a low proportion of them, around 250 and 600 cases, respectively [36]. Based on laboratory virological tests performed at distinct sites nationwide, we estimate that less than one third of T-cell lymphoproliferative syndromes are currently tested for HTLV-1 in Spain. On the other hand, dermatologists rarely ask for HTLV-1 testing in patients presenting with cutaneous T-cell infiltrative cancer lesions. In contrast, neurologists tend to exclude HTLV-1 more frequently as part of the differential diagnosis of patients presenting with subacute paraparesis.

Another cause of underreporting for ATLL could be associated with acute presentations with severe illness, rapid progression to death and unspecific clinical manifestations, patients dying before being diagnosed. In our historical case series, underreporting due to this abrupt clinical outcome could have occurred. However, in more recent times it should be rare since postmortem diagnoses are recorded with full information at the hospital discharge reports [12]. Although incomplete information and management heterogeneity preclude drawing more conclusions, our series of 35 consecutive cases of ATLL recorded over three decades in Spain, a non-endemic country for HTLV-1, describes confidently the main features of this viral neoplasia outside endemic regions.

In summary, we report the main clinical and demographic features of 35 consecutive ATLL patients diagnosed in Spain over three decades. They represented 7.8% of all individuals diagnosed with HTLV-1 in Spain to date. The majority presented with aggressive acute or lymphoma forms and had uniformly very poor prognosis. HTLV-1 screening in non-endemic regions should be performed at least once in all migrants from endemic countries and in natives who had lived in, have mothers from, or sex partners born in such countries, and before organ transplantation. Furthermore, since avoidance of breastfeeding halts vertical transmission to newborns, universal HTLV-1 testing should be part of prenatal screening.

Ethical approval

UNIR ethics committee ref. PI047/2023.

CRediT authorship contribution statement

VS and CdM contributed with conceptualization, data curation, formal analysis, funding, and writing of original draft. All authors contributed with validation of data, review & editing of original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcv.2023.105578.

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