Adult T cell leukaemia/lymphoma in Kerala, South India: are we staring at the tip of the iceberg?

**Rekha A. Nair · Priya Mary Jacob · Sreejith G. Nair ·
Shruti Prem · A. V. Jayasudha · Nair P. Sindhu ·
K. R. Anila**

Received: 17 January 2013 / Accepted: 16 July 2013 / Published online: 2 August 2013
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Abstract This study comes from Regional Cancer Centre, Trivandrum, in the state of Kerala, South India. Regional Cancer Centre is a comprehensive cancer centre catering to the population of the State of Kerala and the adjoining states of Tamil Nadu and Karnataka. This study is an analysis of leukaemic phase, nodal and extranodal presentations of adult T cell leukaemia/lymphoma (ATLL) in our institute. This study aims to document the alarming incidence of ATLL in this part of South India. This study includes 32 cases, which were diagnosed as compatible with ATLL over a period of 26 months. Our diagnostic approach to a typical case starts with a detailed history, clinical examination with emphasis on skin lesions, evaluation of laboratory findings especially serum calcium and lactate dehydrogenase values. A peripheral blood examination would be followed by ancillary tests like flow cytometric immunophenotyping of peripheral blood or histopathological examination with immunostaining of submitted tissue biopsy. The last step is the confirmatory serology test for serum human T cell lymphotropic virus type 1 (HTLV-1) antibody. We report for the first time from the state of Kerala, South India, 15 patients with HTLV-1-positive ATLL. This high incidence of ATLL in our state population hitherto not reported is worrisome and entails routine screening for serum HTLV-1 before invasive procedures and among voluntary blood donors in our population.

Keywords Non-endemic · Adult T cell leukaemia/lymphoma · Kerala, India

Introduction

Adult T cell leukaemia/lymphoma (ATLL) is a lymphoproliferative neoplasm of helper T lymphocytes caused by human T cell lymphotropic virus type 1 (HTLV-1). ATLL is essentially a disease of adults and has a poor prognosis with a median survival time of 13 months, even if multiagent chemotherapy is given. HTLV-1 infection is geographically confined to specific areas such as Japan, the Caribbean basin, South America, Sub-Saharan Africa, Melanesia and the Middle East [1]. There have been a few sporadic case reports from India. This study comes from the state of Kerala in South India where we report 15 patients with HTLV-1-positive ATLL. This study aims to highlight the alarming number of ATLL cases reported for the first time in India and in the state of Kerala, which is not known as a region endemic for HTLV-1.

Subjects and methods

This is a retrospective study of 26 months duration from November 2010 to January 2013. For the period of this study, 1,359 lymphomas were diagnosed at our centre (tissue based data), out of which 197 (14.5 %) were of T cell origin.

A total of 32 cases in which a primary diagnosis of ATLL was made/ suggested based on flow cytometric immunophenotyping of peripheral blood or by immunohistochemistry on tissue biopsies were included in this study.

Morphology

The peripheral blood smears were stained with Giemsa for morphological evaluation. The classical morphological appearance of the cell in ATLL is the “flower cell”, which has highly indented, convoluted or lobulated nuclei with condensed chromatin, small or absent nucleoli and a basophilic and agranular cytoplasm (Fig. 1).

R. A. Nair (✉) · P. M. Jacob · A. V. Jayasudha · N. P. Sindhu ·
K. R. Anila
Department of Pathology, Regional Cancer Centre,
Medical College P.O., Trivandrum 695011, India
e-mail: drrekhanair@gmail.com

S. G. Nair · S. Prem
Department of Medical Oncology, Regional Cancer Centre,
Trivandrum, India

Fig. 1 Giemsa1000 Peripheral smear showing the classical “flower” cells

Immunophenotyping by flow cytometry

Of the total 32 cases, we analysed flowcytometry (FCM) data of 19 cases. The peripheral blood was sent in ethylenediaminetetraacetic acid and was processed for immunophenotyping by FCM. The cells were prepared by whole blood stain, lyse and wash technique. Six-parameter, four-colour immunophenotyping was performed using a FACSCalibur (Becton Dickinson, San Jose, CA, USA). A minimum of 10,000 events were acquired using side scatter versus forward scatter gating. Data were analysed with CellQuestpro software (Becton Dickinson). Fluorochromes used were fluorescein isothiocyanate (FITC), phycoerythrin (PE), peridinin chlorophyll protein and allophycocyanin (APC). A panel of directly conjugated monoclonal antibodies, comprising of CD2 (PE-S5.2), CD3 (APC-SK7), CD7 (FITC-4H9), CD4 (PE-SK3), CD8 (FITC-SKI), CD25 (APC-2A3), CD5 (PE-L17F12), CD19 (PERCP-4G7), CD20 (APC-L27), CD34 (PE-8G12) and CD45 (PERCP-2D1) were used.

Immunohistochemistry on tissue biopsies

A panel of immunohistochemical markers comprising CD3 (clone LN10, Novacastra, New Castle, UK; 1:200 dilution), CD5 (clone 4C7, Novacastra, New Castle, UK; 1:100 dilution), CD7 (clone LP15, Novacastra, New Castle, UK; 1:100 dilution), CD30 (clone Ber-H2, DakoCytomation, Denmark; 1:40 dilution), CD25 (clone 4C9, Novacastra, New Castle, UK; 1:50 dilution) and CD20 (clone L26, DakoCytomation, Denmark; 1:400 dilution) were performed on 5-mm, formalin-fixed, paraffin-embedded sections and processed using automated immunostaining with the Ventana Ultraview DAB detection kit in a Ventana BenchMark XT processor (Ventana Medical Systems, Tucson, AZ, USA).

Testing for serum HTLV-1

Serum HTLV-1 estimation was advised in all cases.

Results

Demography

The age of patients in this study ranged from 40 to 75 years with median age at presentation being 55 years. The male/female ratio was 2:1.

ATLL cases: diagnosed on flow cytometric immunophenotyping of peripheral blood

Nineteen cases were diagnosed as compatible with ATLL based on the acute clinical presentation, immunophenotype and laboratory findings (Table 1). Serum HTLV-1 estimation was done by Western blot method in 13 cases. Out of these, 10 cases were positive and 3 were negative. Out of the 10 HTLV-1-positive cases, 5 cases showed skin lesions, which ranged from a diffuse erythematous rash as in case 16 (of Table 1; Fig. 2) to extensive ulcerating lesions all over the body except face and anterior chest wall as in case 8 (of Table 1; Fig. 3). Flow cytometric immunophenotyping of all the HTLV-1-positive ATLL cases showed classical immunophenotype of CD4+, CD8−, CD3+, CD5+, and CD25+ with loss of CD7, but one case (case 7) was negative for CD5 and CD25 in addition to CD7 (Fig. 4) and one case did not show loss of CD7 (case9). Amongst these 10 cases, serum calcium was raised in 5 cases and serum lactate dehydrogenase (LDH) in 8 cases.

Out of the 19 cases diagnosed by flow cytometry, 8 died within 6 months of diagnosis, 4 cases underwent chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) and are still on follow-up, while in 7 cases, they opted for palliative treatment at a local hospital once the prognosis was explained to them.

A concurrent examination of peripheral blood smear can, at times, solve a diagnostic puzzle. Case 1 is that of a 62-year-old man who presented with generalised lymphadenopathy and extensive skin lesions. This case was unusual because the morphology and immunohistochemical findings on lymph node resembled that of a lymphocyte-rich classical Hodgkin's lymphoma. Concurrent examination of peripheral blood smear revealed classical flower cells, which alerted us to the possibility of an ATLL. Flow cytometry of this peripheral blood sample confirmed the presence of an abnormal T cell population with an ATLL phenotype: CD2+, CD3+, CD5+, CD7−, CD25+, CD4+, and CD8− (Fig. 5). His lymph node biopsy showed sheets of intermediate-sized atypical lymphoid cells (expressing CD3, CD5, CD25 and lacking CD7) with scattered large Reed–Sternberg-like cells, which were positive for CD30, PAX5 and Epstein–Barr encoded RNAs (EBER) and negative for CD15 (Fig. 6a–f). Serum HTLV-1 estimation was positive. The patient received CHOP (6 cycles) at the end of which he did not go into remission. He was then started on palliative chemotherapy with etoposide and prednisolone

Table 1 ATLL cases: diagnosed on flow cytometry of peripheral blood

Serial number	Sex, age (years)	Skin lesions, lymph node and bone lesions	S.LDH value (IU/L)	S.ca (mg/dL)	Immunophenotype on flow cytometry	S.HTLV-1 status by Western blot
1.	M, 62	Skin lesions seen, lymph nodes+	588	8.8	CD4+, CD8–, CD3+, CD5+, CD7–, CD25+	Positive
2.	F, 75	None	1,951	8.5	CD4+, CD8–, CD2+, CD3+, CD5+, CD7–, CD25+	Positive
3.	F, 65	Skin lesions seen	3,500	11	CD4+, CD8–, CD3+, CD5+, CD7–, CD25+	Positive
4.	M, 58	None	2,150	14	CD4+, CD8–, CD2+, CD3+, CD5+, CD7–, CD25+	Positive
5.	M, 68	None	2,249	12.6	CD4+, CD8–, CD2+, CD3+, CD5+, CD7–, CD25+	Positive
6.	M, 55	None	6,934	9.4	CD4+, CD8–, CD3+, CD5+, CD7–, CD25+	Positive
7.	M, 54	None	3,222	14.0	CD4+, CD8–, CD2+, CD3+, CD5–, CD7–, CD25–	Positive
8.	M, 68	Skin lesions seen	529	9.5	CD4+, CD8–, CD2+, CD3+, CD5+, CD7–, CD25+	Positive
9.	M, 70	Skin lesions seen	1,410	8.0	CD4+, CD8–, CD3+, CD5+, CD7+, CD25+	Positive
10.	F, 52	Skin lesions seen	1,930	8.1	CD4+, CD8–, CD2–, CD3+, CD5+, CD7–, CD25–	Not done
11.	M, 48	None	649	9.3	CD4+, CD8–, CD2–, CD3+, CD5+, CD7–, CD25+	Not done
12.	M, 62	None	2,368	11.1	CD4+, CD8–, CD2+, CD3+, CD5+, CD7–, CD25+	Not done
13.	M, 48	Skin lesions seen	704	7.4	CD4+, CD8–, CD2+, CD3+, CD5+, CD7–, CD25+	Not done
14.	F, 55	No skin lesions, lymph nodes+, pathological fracture bone present	1,956	7.6	CD4+, CD8–, CD2+, CD3+, CD5+, CD7–, CD25+	Not done
15.	F, 56	No skin lesions, complained of joint pain	1,575	6.6	CD4+, CD8–, CD2+, CD3+, CD5+, CD7–, CD25–	Negative
16.	M, 53	Skin-diffuse erythematous rash	1,649	17.9	CD4+, CD8–, CD2+, CD3+, CD5+, CD7–, CD25+	Positive
17.	M, 50	Skin lesions seen	812	8.8	CD4+, CD8–, CD2+, CD3+, CD5+, CD7–, CD25+	Negative
18.	F, 50	No skin lesions, lymph nodes+	3,100	8.9	CD4+, CD8–, CD3–, CD5+, CD7–, CD25+	Negative
19.	M, 60	No skin lesions	18,476	8.4	CD4+, CD8–, CD3–, CD5+, CD7–, CD25–	Not done

S.LDH serum lactate dehydrogenase normal reference range=313–618 U/L; S.ca serum calcium normal reference range=8.4–10.2 mg/dL

following which he is still not in remission (7 months since initiation of therapy).

Fig. 2 The patient had a diffuse erythematous rash over neck and anterior chest wall (case 16 of Table 1)

ATLL cases: diagnosed on tissue biopsies

13 cases were diagnosed as compatible with ATLL based on the acute clinical presentation, immunophenotype and laboratory findings (Table 2). Site of biopsies were lymph node (eight cases), skin (three cases), bone (one case) and ileocaecum (one case). HTLV-1 serology was available in seven cases, of which five cases were positive. The skin lesions in all three cases were reddish, nodular and seen all over the body (Fig. 7a, b; case 20 of Table 2). Among the five HTLV-1-positive cases, serum calcium levels were raised in two cases and serum LDH was raised in four cases. The immunohistochemical findings in these cases were classical except for one case (case 32 of Table 2), which showed loss of CD5 in addition to CD7. The only case in this series with the site in the gastrointestinal tract was case 22 (of Table 2). This case was of a 40-year-old man, chronic alcoholic and smoker, presented with loss of weight and loss of appetite of 10 months duration. CT scan abdomen showed circumferential wall thickening in the ileocaecal region. Biopsy from the same showed an infiltrate composed of large cells, which were CD3 positive, CD5 positive, CD25 positive and CD20 negative and showed loss of CD7 (Fig. 8a–f). His peripheral smear was normal except for the presence of occasional tumour cells. Serum HTLV-1 estimation was positive. He was diagnosed as ATLL and started on

Fig. 3 a–c The patient presented with extensive ulcerating lesions all over his body of 1 month duration (case 8 of Table 1)

chemotherapy with CHOP. He completed 6 cycles of the same, following which a CT scan of the abdomen was done (5 months since initiation of therapy), the result of which was normal.

Out of the 13 cases diagnosed on tissue biopsies, 4 patients died within 6 months of diagnosis, 1 case underwent chemotherapy with CHOP and is still on follow-up, while in 8 cases, they opted for palliative treatment at a local hospital.

Discussion

Epidemiology

Endemic areas for the HTLV-1 virus have been identified in the Caribbean basin, parts of Africa, Latin America, the Middle East and the Pacific region. Japanese area-related studies estimated that about one million people are currently infected by HTLV-1 in Japan, while 1–5 % of HTLV-1 aetiologically linked

with ATLL [2, 3]. The three major routes of HTLV-1 transmission are mother to child infections via breast milk, sexual intercourse and blood transfusions [4].

The Indian scenario

A few sporadic cases of ATLL are reported from other parts of the world. There are a few studies and reports from India, but none have reported such a large number of cases. In a study by Roy et al., where 946 healthy volunteers were screened at a single centre in North India, there was no detectable HTLV-1 infection [5]. However, an analysis of blood donors from Mumbai showed a 1.9 % prevalence of HTLV infection [6]. A study from South India showed HTLV-1 prevalence of 3.7 % among HIV-positive patients, while the rate was 0.3 % in the HIV-negative population [7]. Faiq Ahmed et al. reported three cases from Hyderabad, Andhra Pradesh (South Eastern state) [8]. Gujral et al. reported two cases of ATLL from Mumbai,

Fig. 4 Flow cytometric dot plots of case 7 (of Table 1), showing loss of CD5, CD7 and CD25

Maharashtra (Western state), though HTLV serology was done in only one case [9]. Jain et al. reported one case of ATLL from Mumbai, Maharashtra (Western state) [10]. Udupa Karthik et al. reported two cases of ATLL from Chennai, Tamil Nadu (Southern state) [11]. It is interesting to note that majority of cases of ATLL reported from India are from the Southern States.

Aetiopathogenesis

ATLL was first described in 1977 by Uchiyama and Takatsuki as a distinct clinicopathological entity with a suspected viral

etiology because of the clustering of the disease in the south-west region of Japan [12]. Subsequently, a novel RNA retrovirus, HTLV-1, was isolated from a cell line established from leukaemic cells of an ATLL patient, and the finding of a clear association with ATLL led to its inclusion among human carcinogenic pathogens [13, 14]. The crucial role of the viral product Tax in ATLL leukemogenesis was demonstrated [15]. Recently, another HTLV-1 product, HBZ, which is encoded on the negative strand, was found, and it has now become a subject of intensive research because of its possible activity in cell proliferation [16]. Aberrations of tumor suppressor genes

Fig. 5 Flow cytometric dot plots showing immunophenotypic profile of the leukaemic cells of case 1 (of Table 1)

Fig. 6 **a** Haematoxylin and eosin staining $\times 400$. Lymph node biopsy showing large binucleate cells resembling classical Reed–Sternberg cells in a background of atypical small lymphoid cells (*inset* shows Hodgkin’s-like cell) (case 1 of Table 1). **b** CD30, $\times 400$. Hodgkin’s-like cells are CD30 positive. **c** CD5, $\times 400$. Background lymphoid cells are positive for CD5. **d** CD7, $\times 400$. Background lymphoid cells show loss of CD7. **e** EBER, $\times 400$. Hodgkin’s-like cells are positive for EBER. **f** PAX5, $\times 400$. Hodgkin’s-like cells are positive for PAX5

like TCF8 are also profoundly involved in the later stages of ATLL development [17].

Clinical features and diagnosis

ATLL patients show a variety of clinical manifestations because of various complications of organ involvement by ATLL cells, opportunistic infections and/or hypercalcaemia. These three often contribute to the extremely high mortality of the disease. Lymph node, liver, spleen, and skin lesions are frequently observed. Less frequently, digestive tract, lungs, central nervous system, bone and/or other organs may be involved. Large nodules, plaques, ulcers and erythroderma are common skin lesions. Some patients have a chronic or smouldering presentation and less fulminant disease course. The diagnosis of typical ATLL is based on clinical features, ATLL cell morphology, mature helper T cell phenotype and anti-HTLV-1 antibody in most cases [4]. Those rare cases, which might be difficult to diagnose, can be shown to have monoclonal integration of HTLV-1 proviral DNA in the

malignant cells as determined by Southern blotting. However, the monoclonal integration of HTLV-1 is also detected in some HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients and HTLV-1 carriers [18, 19].

In our study, among the 15 HTLV-1 positive cases, serum calcium was raised in only 7 of 15 cases, serum LDH was elevated in 12 of 15 cases and skin lesions were seen in only 7 of 15 cases. Hypercalcaemia was not a common feature among our cases. Three cases showed an unusual immunophenotype. One case (case 7 of Table 1) was CD4+, CD8–, CD2+, CD3+, CD5–, CD7– and CD25–; another case (case 32 of Table 2) was CD3+, CD5–, CD7–, CD25+ and CD20–; while the third case with unusual immunophenotype was case 9 (of Table 1), which was CD4+, CD8–, CD3+, CD5+, CD7+ and CD25+. In a study by Yokote et al., where they studied the immunophenotype of 30 cases of ATLL by flow cytometry, they describe one case that was CD5 and CD25 negative, in addition to being CD7 negative. In their series, they also describe 10 cases that were CD7 positive, CD3 positive, CD5 positive and CD25 negative [20]. Only one of our confirmed cases was

Table 2 ATLL cases: diagnosed on histopathology

Serial number	Sex , age (years)	Skin lesions	LDH	S.Ca	Peripheral blood	Site	IHC findings	S.HTLV-1 status
20	M, 70	Nodular skin lesions seen.	441	9.3	A few tumour cells	Skin nodules	CD3+, CD5+, CD7–, CD25+, CD56–, CD20–	Positive
21	M, 52	–	907	8.3	A few tumour cells	Lymph node	CD3+, CD5+, CD7–, CD30–, CD25+	Positive
22	M, 40	–	886	9.6	A few tumour cells	Ileocaecum	CD3+, CD5+, CD7–, CD25+, CD20–	Positive
23	M, 45	Skin lesions seen.	1,154	19	Tumour cells ++	Skin nodules	CD3+, CD5+, CD7–, CD25+	Positive
24	M, 57	–	1,276	8.7	Normal	Lymph node	CD3+, CD5+, CD7–, CD25+	Not done
25	F, 52	–	5,202	Not done	Normal	Lytic lesion, Left trochanter.	CD3–, CD5+, CD7–, CD25+	Not done
26	F, 47	–	426	18	Normal	Lymph node	CD3+, CD5+, CD7–, CD30–, CD25+	Negative
27	M, 70	–	Not done	8.8	A few tumour cells	Lymph node	CD3+, CD5+, CD7–, CD25+, CD20–	Negative
28	M, 45	–	6,862	10.9	Tumour cells++	Lymph node	CD3+, CD5+, CD7–, CD25+	Not done
29	M, 62	–	1,860	9.7	Few atypical cells	Lymph node	CD3+, CD5+, CD7–, CD25+, CD20–	Not done
30.	M, 71	Skin lesions seen	896	9.8	A few tumour cells	Skin nodule, Lymph node	CD3+, CD5+, CD7–, CD25+	Not done
31	F, 55	–	3,746	Not done.	A few tumour cells	Lymph node	CD3+, CD5+, CD7–, CD25+, CD20–	Not done
32	F, 43	–	1,424	11	A few tumour cells	Lymph node	CD3+, CD5–, CD7–, CD25+, CD20–	Positive

S.LDH serum lactate dehydrogenase normal reference range=313–618 U/L; *S.ca* serum calcium normal reference range=8.4–10.2 mg/dL

CD25 negative. They also classify their cases into four clinical subtypes: acute type (73 %), chronic type (4 %), lymphoma type (12 %) and smouldering type (12 %). Among our 15

confirmed cases, 12 were acute type (80 %) and 3 were of lymphoma type (20 %).

In our series of cases, HTLV-1 testing was not done in 12 cases. Five cases that were HTLV-1 negative were also included because, based on clinical features and immunophenotype, these were highly suspicious for ATLL. These cases may not be ATLL. They could be the leukaemic phase, nodal or extranodal presentations of a peripheral T cell lymphoma, NOS or angio-immunoblastic T cell lymphoma until otherwise proved.

Testing for HTLV

It has been estimated that, worldwide, 10–25 million people are infected with HTLV-1 retrovirus [2, 3]. Most HTLV-1-infected individuals remain asymptomatic throughout their lifetimes. However, 5–10 % of infected people develop clinical complications, among which ATLL and HAM/TSP are the most severe. Other manifestations of HTLV-1 infection include infective dermatitis, uveitis, arthritis and *Strongyloides stercoralis* infection [3, 21–23].

HTLV-2 is endemic in Amerindian and pygmy populations and epidemic in intravenous drug users. In contrast to the case for HTLV-1, convincing epidemiological demonstrations of a definitive aetiological role of HTLV-2 in human disease are limited [24, 25]. In due course, two more genotypes, HTLV-3 and HTLV-4, were discovered in asymptomatic individuals from Cameroon. To date, no diseases have been reported in association with HTLV-3 or HTLV-4 [26–28]. Further research is needed to determine the distribution and prevalence as well as the pathogenicity of these two new genotypes. The routine

Fig. 7 **a, b** The patient presented with reddish nodules of varying sizes all over body (case 20 of Table 2)

Fig. 8 **a** H&E, $\times 100$. Biopsy from ileocaecal wall thickening (case 22 of Table 2). **b** H&E, $\times 400$. Diffuse infiltration by tumour cells is seen. **c** CD3, $\times 400$. Tumour cells are CD3 positive. **d** CD5, $\times 400$. Tumour cells are CD5 positive. **e** CD7, $\times 400$. Tumour cells show loss of CD7. **f** CD25, $\times 400$. Tumour cells are CD25 positive

diagnosis of HTLV infections is based on conventional serological techniques such as enzyme-linked immunosorbent assay and Western blotting. However, among samples infected with HTLV-1 or HTLV-2, the proportion of seroindeterminate results is high [29]. Moreover, in the cases of HTLV-3 and HTLV-4, an indeterminate Western blot pattern appears to be the rule rather than the exception [26, 30]. This led to the development of more sensitive molecular techniques. Polymerase chain reaction methods (commercially available and in-house modified tests) represent the gold standard useful to obtain a high level of specificity and reproducibility in a short time as they establish the presence of the genome and its modulation over time and/or in the presence of specific therapy [31, 32].

Epstein–Barr virus infected B immunoblasts in ATLL

Case 1 of this study presented as an overt ATLL involving blood, bone marrow and lymph nodes, which showed Reed–Sternberg-like cells with EBER positivity. A study by Ohtsubo et al. states that the Epstein–Barr virus (EBV) positivity in these cells most likely stems from the underlying immunodeficiency

state precipitated by HTLV-1 infection. CD21 is the EBV receptor and is reported to be over-expressed in CD4⁺ T cells in ATLL as a result of the stimulatory influence of the HTLV-1 Tax protein; however, evidence of EBV DNA integration could not be demonstrated in these cells, questioning the role of EBV in ATLL leukemogenesis [33, 34]. In contrast, a recent study by Ueda et al. purports that co-infection with HTLV-1 and EBV may be associated with a greater likelihood of organ involvement and a more aggressive course through the enhanced expression of adhesion molecules via increased interleukin-4 (IL-4) signalling [33, 35]. The frequency of co-infection of EBV in ATLL has been reported as 17 % [33–35]. Plausibly, patients with ATLL may be more susceptible to this infection than patients with other types of lymphoma due to the levels of immunosuppression. This case illustrates the fact that pathologists need to be attuned to the presence of these Epstein–Barr virus infected B immunoblasts, which can be mistaken for Reed–Sternberg-like cells in the context of ATLL. Before signing out a report of lymphocyte-rich classical Hodgkin's lymphoma in a patient from Southern India, it would be prudent to have a closer look at the background lymphoid population and the peripheral blood smear.

Stumbling blocks

Some of the stumbling blocks that we faced while undertaking this study are listed as follows:

1. At present, serum HTLV-1 estimation by Western blot is an expensive investigation for most patients. There is no routine screening for serum HTLV-1 in any of the government institutions because Kerala or South India is not recognised as a state with a high incidence of ATLL. In our study in a significant number of suspicious cases, testing for HTLV-1 was not done because the patients could not afford this investigation.
2. The method used for serum HTLV-1 estimation in this study is Western blot. In those cases that are negative on Western blot, in which a strong clinical suspicion exists, other methods of estimation like PCR are indicated, which are currently not available with us. In those cases that are negative by PCR, a different strain of the HTLV virus needs to be looked for.
3. There is, to a certain extent, a lack of awareness about this disease among clinicians in peripheral local hospitals who refer cases to us. Keeping in mind the incidence of ATLL in our state and the potential for learning more about the transmission of HTLV-1 in Kerala, it is recommended that physicians who see adults with diffuse non-Hodgkin's lymphoma with at least two features consistent with ATLL (abnormal lymphocytes on peripheral blood smear, T cell phenotype of malignant cells, visceral involvement, hypercalcaemia, lytic bone lesions and skin lesions) are encouraged to report these cases through their local and state health department or refer these to our centre for further workup and confirmation.

Kerala—a new hotspot

This study shows a very high occurrence of ATLL cases from the Indian subcontinent, which has never been reported before. This high incidence of ATLL in our population is a cause for concern and entails routine screening for serum HTLV-1 before invasive procedures and among voluntary blood donors in our population. The purpose of this study is a clarion call to the concerned authorities. Epidemiological surveillance to document this alarming trend is the need of the hour. The epidemiology of HTLV-1 infection could change in the near future, in the wake of emigration. Epidemiological surveillance and correct diagnosis are recommended to verify the prevalence and incidence of a new and undesirable phenomenon. We are probably staring at the tip of the iceberg.

Acknowledgement Dr Mammen Chandy, eminent haematologist, presently Director, Tata Medical Center, Kolkata, India, for a thoughtful comment he made during a conference that most cases of ATLL he had seen

were from the state of Kerala. Department of Radiotherapy, Medical college, Trivandrum for clinical photographs Fig. 3a–c. A part of this study was presented as a poster titled “Adult T-cell leukaemia / lymphoma (ATLL)—hot spot in South India” at the XVI Meeting of the European Association for Haematopathology October 20th–25th, 2012 in Lisbon, Portugal.

Conflict of interest The authors declare that they have no conflict of interest.

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