DERMATOLOGY PRACTICAL & CONCEPTUAL
www.derm101.com

Adult T-cell leukemia/lymphoma: a case report of primary cutaneous tumoral type

Julia Ocampo Lyra-da-Silva, M.D.[1], Yung Bruno de Mello Gonzaga, M.D.[2], Otávio de Melo Espíndola, M.D.[3], Maria José de Andrada-Serpa, M.D.[3], Cassio Dib, M.D.[3], Thiago Jeunon, M.D.[1,4]

[1] Department of Dermatology, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil
[2] Department of Hematology, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil
[3] Laboratório de Pesquisa em Patogenia Viral do Instituto de Pesquisa Clínica Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil
[4] Department of Anatomical Pathology, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil

Key words: T-cell leukemia/lymphoma, ATLL, lymphoma

Citation: Lyra-da-Silva JO, Gonzaga YBM, Espíndola OM, Andrada-Serpa MJ, Dib, Cassio, Jeunon T. Adult T-cell leukemia/lymphoma: a case report of primary cutaneous tumoral type. Dermatol Pract Conc. 2012;2(2):3. http://dx.doi.org/10.5826/dpc.0202a03.

Received: November 21, 2011; **Accepted:** February 25, 2012; **Published:** April 30, 2012

Funding sources: None.

Conflict of interest: None.

Corresponding author: Thiago Jeunon, M.D., Rua General Roca 778/1005 Saens Peña, Rio de Janeiro, Brasil, CEP 20521-070. Tel. +55 21 97377993; Fax. 22340722. E-mail: thiago.jeunon@gmail.com.

ABSTRACT

Background: Adult T-cell leukemia/lymphoma (ATLL) is a distinctive peripheral T- lymphocytic malignancy associated with human T-cell lymphotropic virus type 1 (HTLV-1). It may closely resemble other skin lymphomas, particularly mycosis fungoides (MF).

Case report: A 38-year-old woman presented some ellipsoid scaling patches lasting 18 months and developed a large tumoral lesion in the abdomen, which were previously diagnosed as MF. Although histopathologic and immunohistochemistry findings were in consonance with this diagnosis, the fast progression of the disease raised the suspicion that it could represent another type of T-cell lymphoma. The work-up revealed a positive anti-HTLV-1 serology and molecular studies confirmed the monoclonal integration of HTLV-1 provirus into neoplastic cells of the skin, but not into circulating lymphocytes. Extensive investigations were unable to demonstrate any systemic involvement. The final diagnosis was of primary cutaneous type of ATLL. The patient was submitted to a chemotherapy regimen with cyclophosphamide, doxorubicin, vincristine and prednisone, later to conjugated dexamethasone and surgical cytoreduction and then to a second line treatment with gemcitabine, resulting in partial response. A bone marrow heterologous transplantation was performed, but failed to achieve a sustained remission.

Discussion: ATLL is a rare lymphoid malignancy in non-endemic HTLV-1 areas, the diagnosis of which could be missed if not highly suspected. In addition to the four subtypes of Shimoyama classification (acute, lymphomatous, chronic and smoldering), a fifth one denominated primary cutaneous and characterized by presence of lesions only in the skin had been proposed and is herein exemplified.

TABLE 1. Clinical forms of ATLL

	Acute	lymphoma	chronic	smoldering	Cutaneous	
					Erythemato-papular	Tumoral
Prevalence	60%	20%	15%	5%	unknown	unknown
MST*	Months to a year	Months to a year	years	>5 years	60 months	19 months
LDH**	elevated	elevated	> 2x the normal upper limit	>1,5 x the normal upper limit	<1,5x the upper limit	<1,5x the upper limit
Hypercalcemia	+	+ or-	-	-	-	-
PB	+	<1%	>5%	>5% or <5% with a histologically-proven skin and/or pulmonary lesions should be present	<5%	<5%
Lymphocytosis	+	-	+	-	-	-
BM****	35% of cases		-		-	-
Lymphadenopathy	+	+	+	-	-	-
Skin lesions	+/-	+/-	+/-	+/-	+	+

*Median survival time **Lactate dehydrogenase ***Peripheral blood circulating lymphocytes with highly abnormal convoluted nuclei ****Bone marrow involvement

Introduction

Lymphomas may involve the skin primarily, when there is no extracutaneous disease by the time of the diagnosis, or secondarily, as an infiltration of a lymphoma from another site, most often lymph nodes [1,2]. Mycosis fungoides (MF) is the most common primary cutaneous lymphoma, accounting for almost 50% of cases of lymphoma restricted to the skin. It is characterized by an indolent course, evolving from patches to plaques and rarely eventuating in tumors over the course of years or even decades [3,4].

Adult T-cell leukemia/lymphoma (ATLL) is a lymphoid malignancy etiologically related to human T-cell lymphotropic virus type 1 (HTLV-1) infection. It is frequently a multi- systemic disease and has been classically classified by Shimoyama et al. into four subtypes, namely acute, lymphomatous, chronic and smoldering [5]. Later, the concept of primary cutaneous ATLL has been set forth, with further subdivision into primary cutaneous erythematopapular (also called primary cutaneous smoldering) and primary cutaneous tumoral (PCT) [6,7,8].

Although not included in the 2005 WHO-EORTC and 2008 WHO classifications, primary cutaneous forms of ATLL seem to have clinical, virological and prognostic particularities and deserve attention of the medical community. Table 1 summarizes the features of clinical forms of ATLL.

Case report

In October 2009, a 38-year-old woman from Macapá/AP was referred to our hospital in Rio de Janeiro/RJ with the diagnosis of MF. For about eight months, she had noted some asymptomatic round and ovoid reddish brown scaling patches on the abdomen and axilla and a large dome-shaped tumoral lesion on right flank, measuring approximately 15

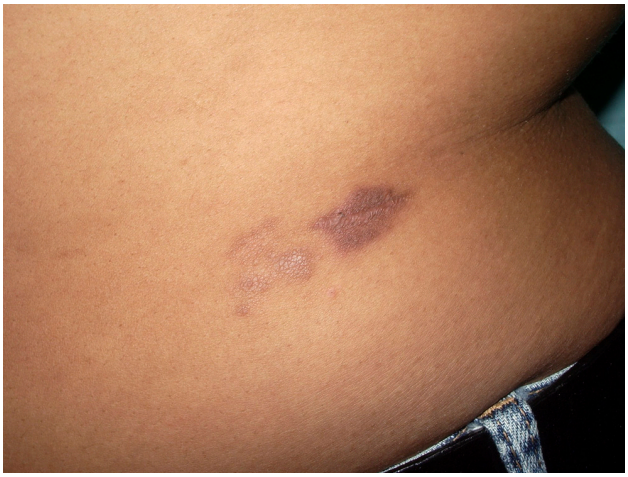

Figure 1. Two reddish-brown, slightly scaling patches on the left flank. The scar in the lesion on the right indicates a biopsy site. [Copyright: ©2012 Lyra-da-Silva et al.]

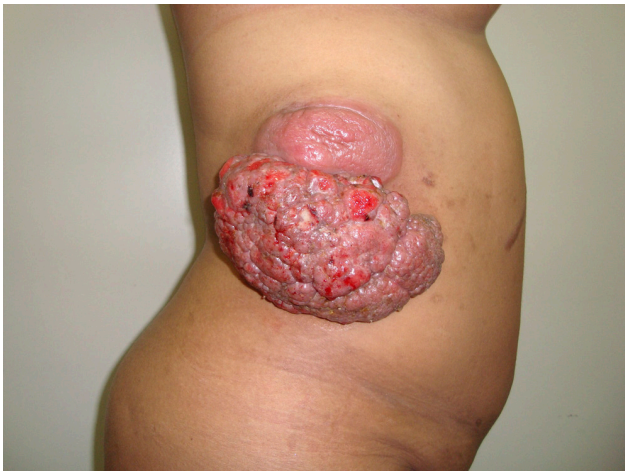

Figure 2. A large dome-shaped tumoral lesion on right flank. The surface is convoluted and focally eroded. [Copyright: ©2012 Lyra-da-Silva et al.]

cm at greatest diameter (Figures 1 and 2). It should be highlighted that the woman had three blood transfusions eight years prior as consequence of a polytrauma.

The patient brought a pathology report dated April 2009 suggesting MF, but the original slides and paraffin blocks were not available. Therefore, we decided to collect new samples. Sections of tissue from a flat lesion showed a superficial perivascular infiltration of small atypical cerebriform lymphocytes that tended to be arranged in band-like array in the dermis and that formed formidable collections in the epidermis (Figure 3). In the tumoral lesion, in addition to the epidermotropism, there was a sheet of medium and large sized cerebriform lymphocytes in the dermis, with many typical and atypical mitotic figures and destruction of adnexal structures (Figure 4).

Immunohistochemistry revealed positivity of neoplastic cells to vimentin, CD3, CD4, CD5, CD7 and negativity to CD20, CD8, CD30, ALK, S-100, Melan-A and AE1-AE3 (Figure 5). Although these findings were in consonance with the diagnosis of MF, the unexpected clinical course raised the suspicion that we could be dealing with another type of T-cell lymphoma.

A work-up, including complete physical exam, blood count, complete biochemistry encompassing serum calcium and lactate dehydrogenase (LDH), chest X-ray, and thorax and abdominal computed tomography scans were unable to demonstrate any systemic involvement. No abnormal lymphocytes were detected on blood smears. Serological tests were negative for HIV and for hepatitis B and C viruses, but positive for HTLV-1. These findings strongly suggested the possibility of ATLL and motivated molecular studies using real-time quantitative polymerase chain reaction (qPCR) to determine the HTLV-1 proviral load in skin lesion and in peripheral blood (PB) [9]. Inverse-long PCR (IL-PCR) [10] was also done to demonstrate monoclonal integration of HTLV-1 proviral DNA into neoplastic cells in skin and blood samples. In addition, multiplex PCR for detection of monoclonal recombination in the gamma chain of T cell receptor (TCR) [11] was performed to confirm transformation of T-lymphocytes. The proviral load was of 20.65% in cells from the skin and less than one infected cell for 10,000 leukocytes in PB. The monoclonal integration was present in the skin sample and absent in the blood sample (Figure 6).

The final diagnosis was of primary cutaneous type of ATLL. Initially, the patient was treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy regimen. At the end of the sixth cycle, there was a poor response, with relapses between each cycle. Thus, cytoreduction with dexamethasone and partial excision of the tumor followed by a second-line treatment with gemcitabine was tried, but also failed to induce disease remission. Remarkably, in spite of the poor response to all therapeutic regimens, the patient did not experience fever, signs of infection, lymphadenopathy, visceromegaly or increase in serum calcium or LDH levels. Considering the unfavorable prognosis and the lack of response to previous therapies, heterologous peripheral blood stem cell transplantation from an HLA compatible brother was successfully done on April 2011, after conditioning chemotherapy with reduced intensity using cyclophosphamide and fludarabine. After the transplant the patient was monitored for three months, but the lesions progressed and showed no response to therapy, even after three additional donor lymphocyte infusions. Thus, the patient will require another hospitalization for salvage chemotherapy (DHAP scheme) and to evaluate if another donor lymphocyte infusion or a bone marrow transplantation should be performed, or if we have arrived at the end of curative efforts.

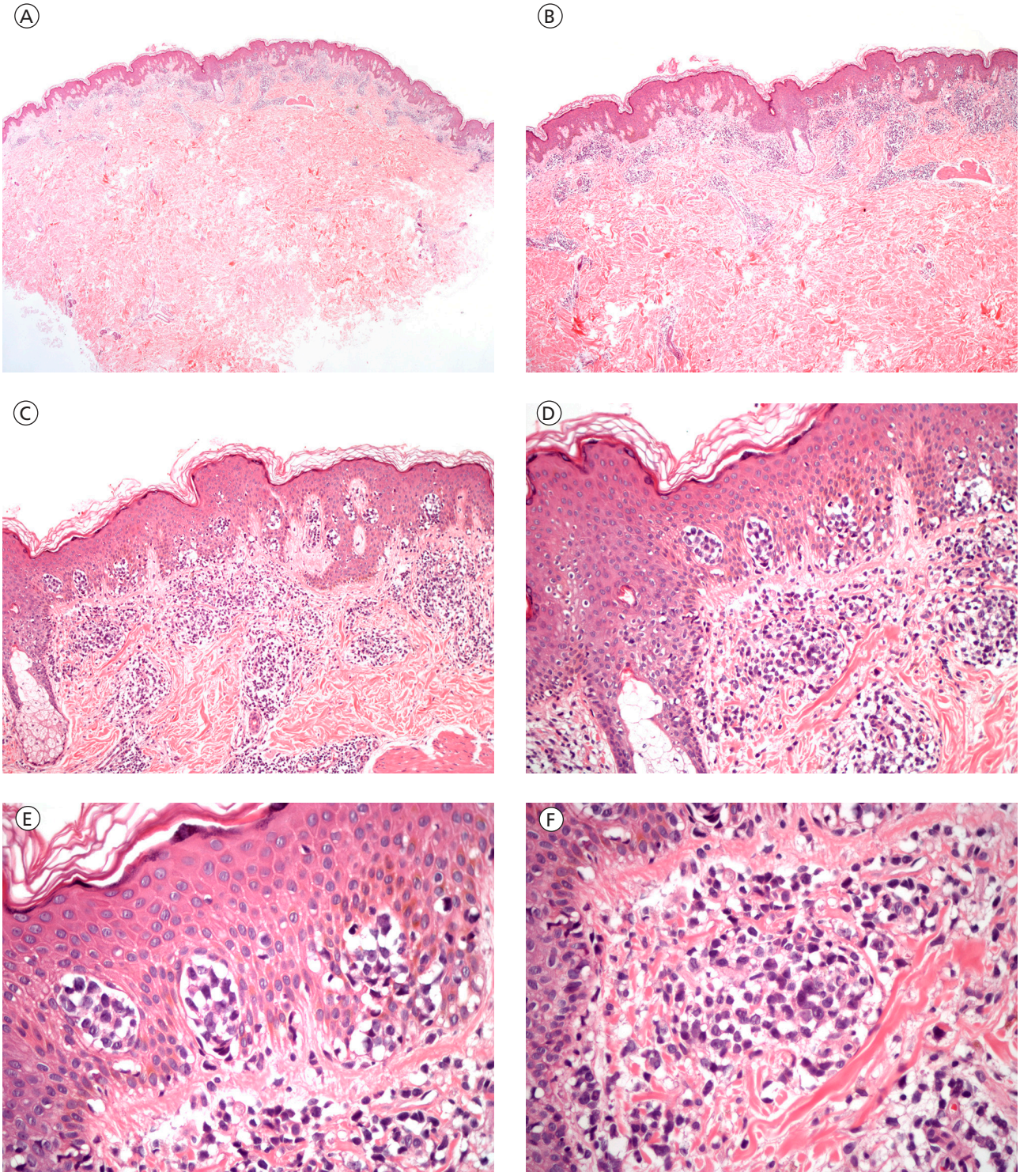

Figure 3. Photomicrograph of a patch: there is a superficial perivascular infiltrate of small atypical cerebriform lymphocytes tending to a band-like array in the dermis and forming collections into the epidermis. There is no spongiosis. Hematoxylin & eosin (HE), (A) 20x, (B) 40x, (C) 100x, (D) 200x, (E) 400x, and (F) 400x. [Copyright: ©2012 Lyra-da-Silva et al.]

Discussion

ATLL is a rare T-lymphocytic malignancy, which occurs mainly in adults. It has a poor prognosis and is remarkably resistant to several therapies. ATLL is related to HTLV-1 infection and the expression of provirus integrated into T-lymphocytes plays a major role in transformation of those cells. The mechanisms through which HTLV-1 infection induces the development of ATLL are complex and involve the interaction of viral protein Tax with cellular factors and activation of transcription pathways controlled by NF-κβ, AP-1 and SRF for example. Tax protein also interferes with function of p53, p16 and MAD1, preventing infected T-cells to undergo cell cycle arrest by DNA damage checkpoints or induction of apoptosis, thus inducing genetic instability. The activity of cytotoxic T-cell lymphocytes is crucial for con-

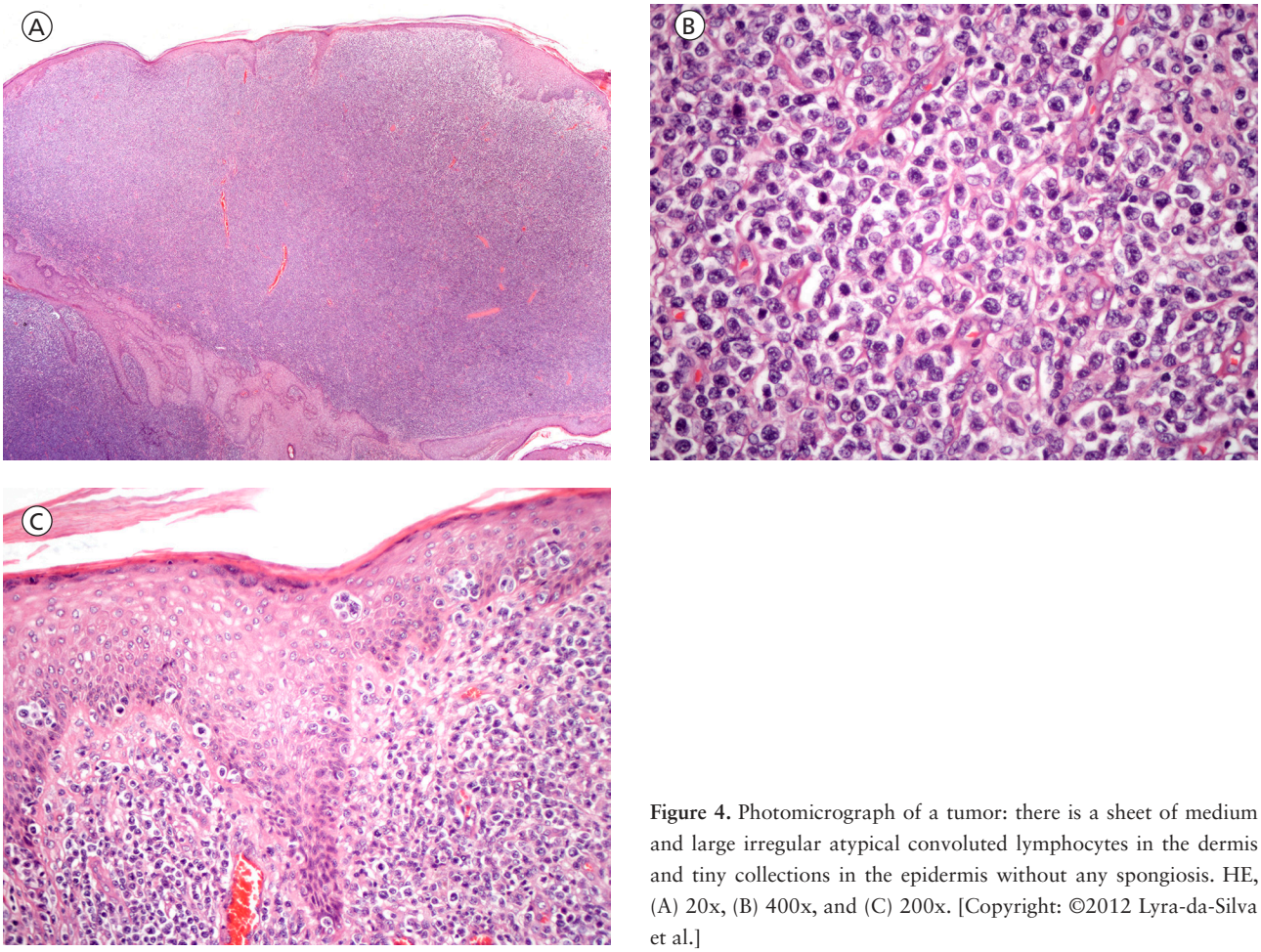

Figure 4. Photomicrograph of a tumor: there is a sheet of medium and large irregular atypical convoluted lymphocytes in the dermis and tiny collections in the epidermis without any spongiosis. HE, (A) 20x, (B) 400x, and (C) 200x. [Copyright: ©2012 Lyra-da-Silva et al.]

trolling viral replication and proliferation of infected cells in vivo. Therefore, inefficiency of the immune host control is an important step in the development of ATLL [12]. The inflammatory response elicited by host immune system is responsible for other manifestations of HTLV-1 infection, such as infective dermatitis, uveitis and tropical spastic paraparesis/HTLV-1 associated myelopathy. HTLV-1 infection is endemic in southwestern Japan, the Caribbean basin and parts of Central Africa and South America. In Brazil, the highest HTLV-1 seroprevalence is seen in Bahia and Rio de Janeiro states [1]. HTLV-1 may be transmitted vertically through placental circulation, during the delivery and breast-feeding period, or horizontally by sexual intercourse, syringe sharing and contaminated blood derivatives. The cumulative risk for development of ATLL among HTLV-1 carriers in Japan is estimated to be around 6.6% for males and 2.1% for females, indicating that most infected persons do not develop disease and the transformation of infected cells occurs after a period of latency of up to 60 years [13].

We could not determine exactly the route of HTLV-1 transmission to our patient, since we were unable to test the mother. However, her brothers were seronegative. Since the patient received blood transfusions in 2003, we suspect that infection was horizontally transmitted. This relatively short latency is in consonance with the epidemiological data about ATLL in Brazil, indicating a shorter latency and younger age of onset for ATLL (median 40 years old, ranging from 2 to 94 years old) in contrast to the worldwide experience [14].

HTLV-1 serology is an excellent screening test for ATLL and must be part of the investigative work in any patient under initial evaluation for a T-cell lymphoma. Considering that infection by HTLV-1 is a prerequisite for development of ATLL, seronegativity excludes this disease [15]. However, it is conceivable that an asymptomatic carrier of HTLV-1 could present a T-cell lymphoma of other types, particularly in endemic areas. This concern is reinforced by the fact that a minority of HTLV carriers develops ATLL during their lives and that ATLL may closely resemble others lymphomas and vice versa. In this context, we strongly recommend that, whenever it is possible, a definitive diagnosis of ATLL must be sustained by demonstration of monoclonal integration of HTLV-1 provirus into neoplastic cells by IL-PCR or Southern blot. Monoclonal integration of HTLV-1 is found in most of the cases of ATLL.

Specific cutaneous lesions occur in 43-72% of cases of ATLL [7] and might be observed in any subtype of the disease. The primary cutaneous ATLL is defined by the presence of skin lesions of ATLL in the absence of lymphadenomegaly, lymphocytosis, hypercalcemia or any involvement of internal organs. Further stratification into primary cutane-

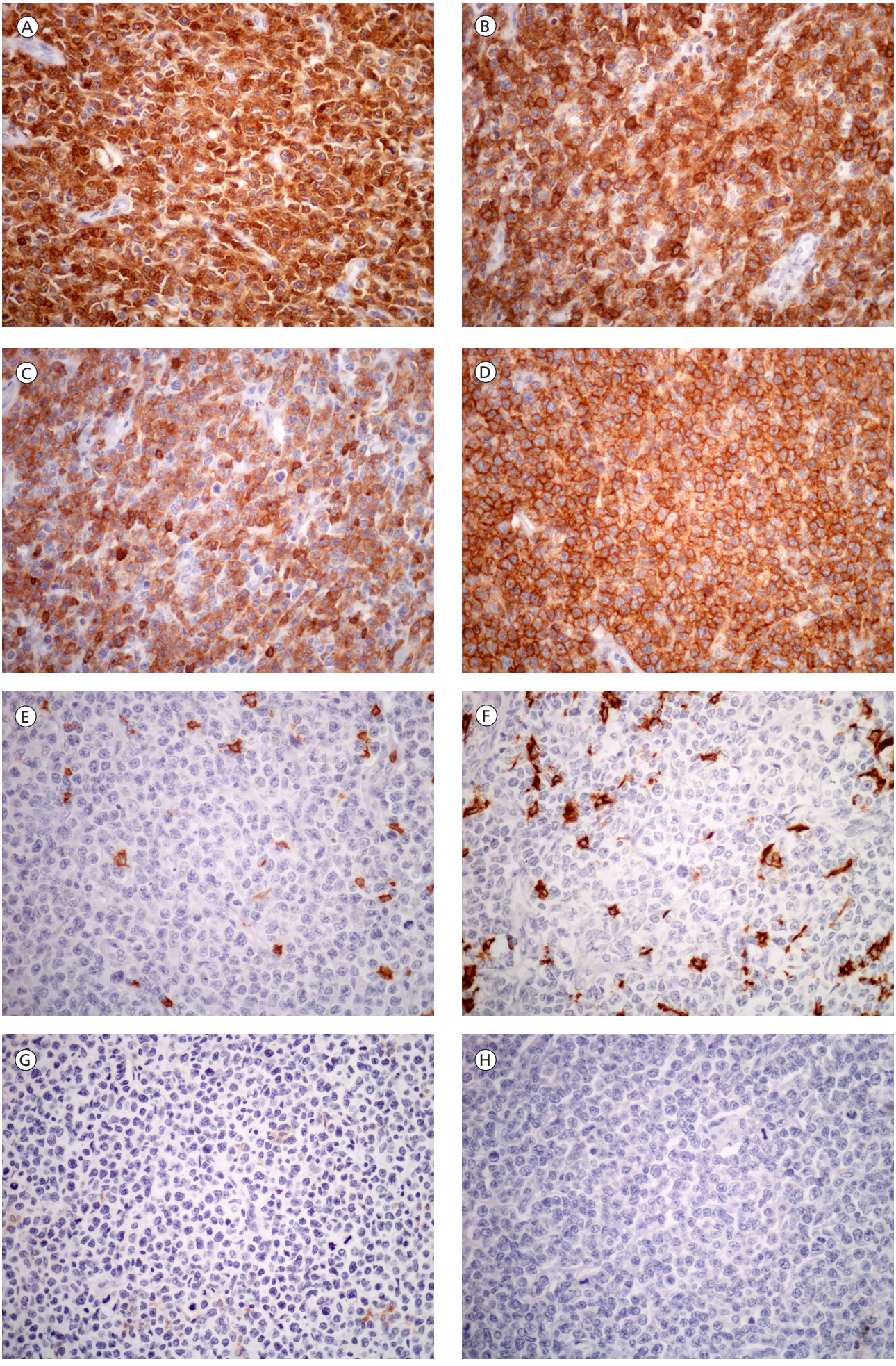
A
B
C
D
E
F
G
H

Figure 5 (previous page). Immunohistochemistry. (A) CD3, (B) CD 5, (C) CD7, (D) CD4, (E) CD8, (F) CD20, (G) CD30, and (H) ALK. [Copyright: ©2012 Lyra-da-Silva et al.]

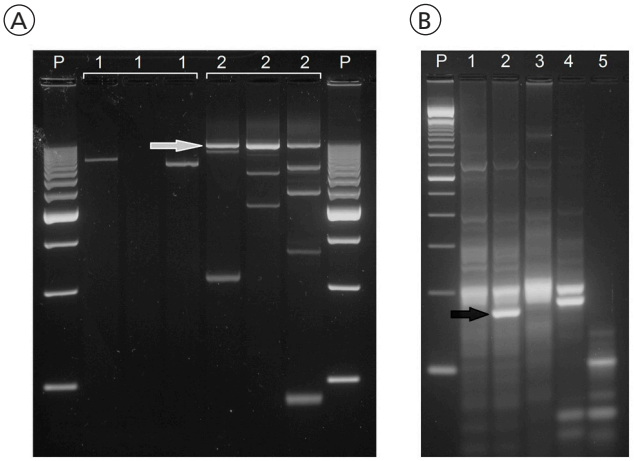

Figure 6. Molecular diagnosis of ATLL. (A) Agarose gel eletrophoresis of amplicons from inverse long PCR (IL-PCR). The IL-PCR was performed in triplicates according to Etoh et al with DNA from: 1, peripheral blood leukocytes; 2, skin lesion. The arrow indicates a monoclonal band for the site of HTLV-1 integration into cellular DNA, which was present only in cells from the skin lesion. P, 500bp DNA ladder. (B) Multiplex PCR for detection of T-cell receptor (TCR) gamma chain gene rearrangements. The assay was performed as described by Fodinger et al with DNA extracted from: 1, peripheral blood leukocytes from the patient; 2, skin lesion; 3, leukocytes from a healthy donor, as a negative control; 4, HTLV-1-infected cell lineage MT2, as a positive control. Healthy individuals show a polyclonal pattern, which is seen as a smear. In line 2, the arrow indicates a band that represents a predominant clonal population of T-cells with a unique rearrangement of TCR-gamma chain, which suggests a malignant process of T- cells. Line 5, no template control and P, 100bp DNA ladder. [Copyright: ©2012 Lyra-da-Silva et al.]

ous erythematous-papular and primary cutaneous tumoral forms is supported by differences in median survival time (60 versus 19 months) [7]. In 2009, Bittencourt et al found very similar results in Bahia [6].

In summary, ATLL is a T-cell lymphoma with variable clinical presentation, which frequently involves the skin. It may be misdiagnosed as other primary cutaneous T-cell lymphomas, especially in the absence of any systemic involvement. In this context, it is crucial to be aware of the primary cutaneous forms of ATLL, which are still not contemplated in the 2008 WHO classification of lymphomas. Proper serological and molecular studies for HTLV-1 are essential to confirm or exclude this possibility. ATLL has a poor prognosis and a remarkable refractoriness for several chemotherapies and even bone marrow transplantation, requiring multidisciplinary attention for optimal management.

References

1. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon: IARC Press, 2008.
2. Burg G, Kempf W, Cozzio A, et al. WHO–EORTC classification of cutaneous lymphomas. In: Weedon D, Leboit P, Burg G, , Sarasin A (eds.). *Pathology and Genetics of Tumours of the Skin*. Lyon: WHO IARC, 2005.
3. Ackerman AB, Jeunon T, Millete F. Advanced dermatopathology: Small-plaque parapsoriasis, like large-plaque parapsoriasis, is mycosis fungoides. Dermatopathology: Practical & Conceptual. 2009;15(2):6.
4. Ackerman AB, Denianke K, Sceppa J, et al. *Mycosis Fungoides: Perspective Historical Allied with Critique Methodical for Illumination Maximal*. New York: Ardor Scribendi, Ltdl, 2008.
5. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T- cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol. 1991;79(3):428-37.
6. Bittencourt AL, Barbosa HS, Vieira MD, Farré L. Adult T-cell leukemia/lymphoma (ATL) presenting in the skin: clinical, histological and immunohistochemical features of 52 cases. Acta Oncol. 2009;48(4):598-604.
7. Amano M, Kurokawa M, Ogata K, Itoh H, Kataoka H, Setoyama M. New entity, definition and diagnostic criteria of cutaneous adult T-cell leukemia/ lymphoma: human T-lymphotropic virus type 1 proviral DNA load can distinguish between cutaneous and smoldering types. J Dermatol. 2008;35(5):270-5.
8. Yamaguchi T, Ohshima K, Karube K, et al. Clinicopathological features of cutaneous lesions of adult T-cell leukaemia/lymphoma. Br J Dermatol. 2005;152(1):76-81.
9. Silva MT, Harab RC, Leite AC, Schor D, Araujo A, Andrada-Serpa MJ. Human T lymphotropic virus type 1 (HTLV-1) proviral load in asymptomatic carriers, HTLV-1-associated myelopathy/tropical spastic paraparesis, and other neurological abnormalities associated with HTLV-1 infection. Clin Infect Dis. 2007;44(5):689-92.
10. Etoh K, Tamiya S, Yamaguchi K, et al. Persistent clonal proliferation of human T- lymphotropic virus type I-infected cells in vivo. Cancer Res. 1997;57(21):4862-7.
11. Fodinger M, Buchmayer H, Schwarzinger I et al. Multiplex PCR for rapid detection of T-cell receptor-gamma chain gene rearrangements in patients with lymphoproliferative diseases. Br J Haematol. 1996;94(1):136-9.
12. Matsuoka M. Human T-cell leukemia virus type I (HTLV-I) infection and the onset of adult T-cell leukemia (ATL). Retrovirology. 2005;2:27.
13. Arisawa K, Soda M, Endo S, et al. Evaluation of adult T-cell leukemia/lymphoma incidence and its impact on non-Hodgkin lymphoma incidence in southwestern Japan. Int J Cancer. 2000;85(3):319-24.
14. Silva FA, Meis E, Dobbin JA, Oliveira MSP. Leucemia-linfoma de células T do adulto no Brasil: epidemiologia, tratamento e aspectos controversos. Rev Bras Cancerol. 2002;48(4):585-95.
15. Tsukasaki K, Hermine O, Bazarbachi A, et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. J Clin Oncol. 2009;27(3):453-9.