P3- HTLV+ LYMPHOPROLIFERATIVE DISEASES

Research Group: Leucemias/linfomas e lesões pre-linfomatosas associados à vírus na Bahia

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No conflicts of interest

APOYO

HTLV1 INFECTION - GENERAL ASPECTS

- Retrovirus, lymphotropic, oncogenic (1980)
- Infects about 10 -20 million people worldwide
- Infection is endemic in regions of Japan, Papua New Guine, Africa, Jamaica and Brazil
- Transmission: Vertical (by breastfeeding); blood and sexual
- Related to a spectrum of diseases, lymphoproliferative and non-lymphoproliferative

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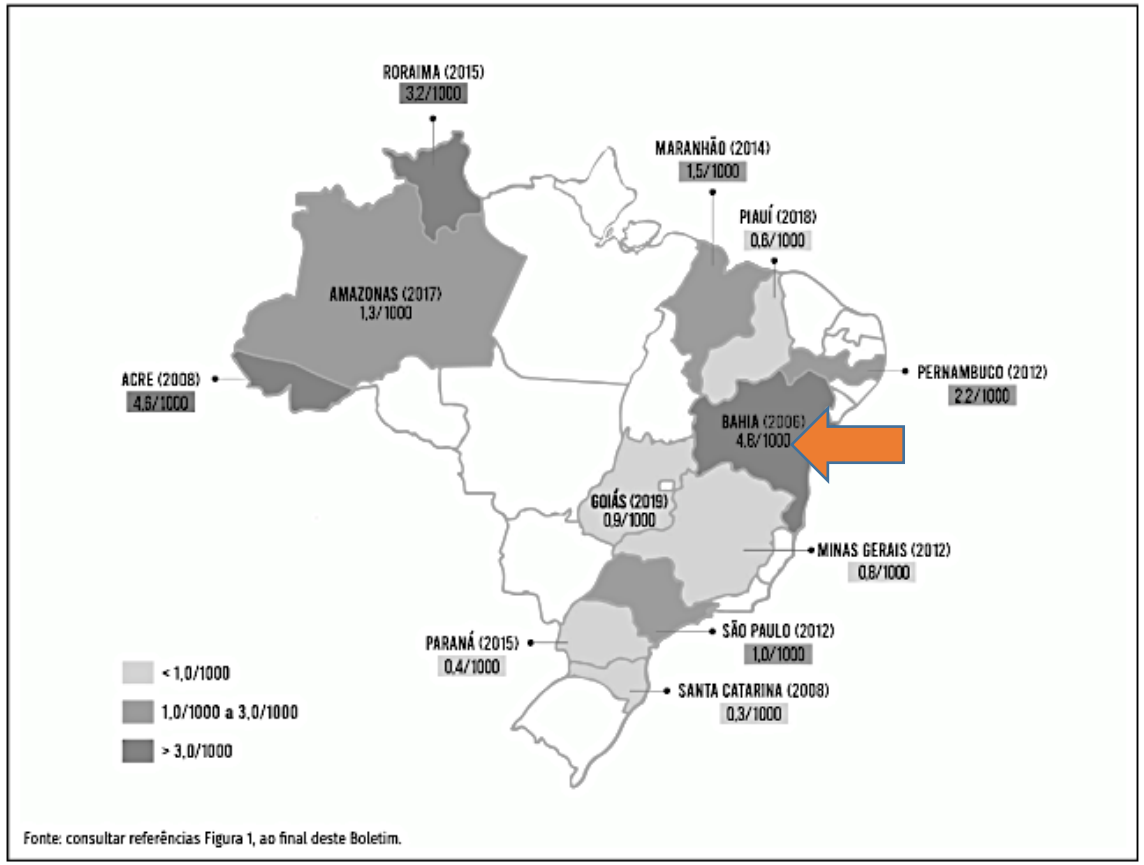


Fonte: consultar referências Figura 1, ao final deste Boletim.

FIGURA 1 Taxas de prevalência (por 1.000) da infecção por HTLV-1/2 em doadores de sangue de 12 capitais de estados brasileiros

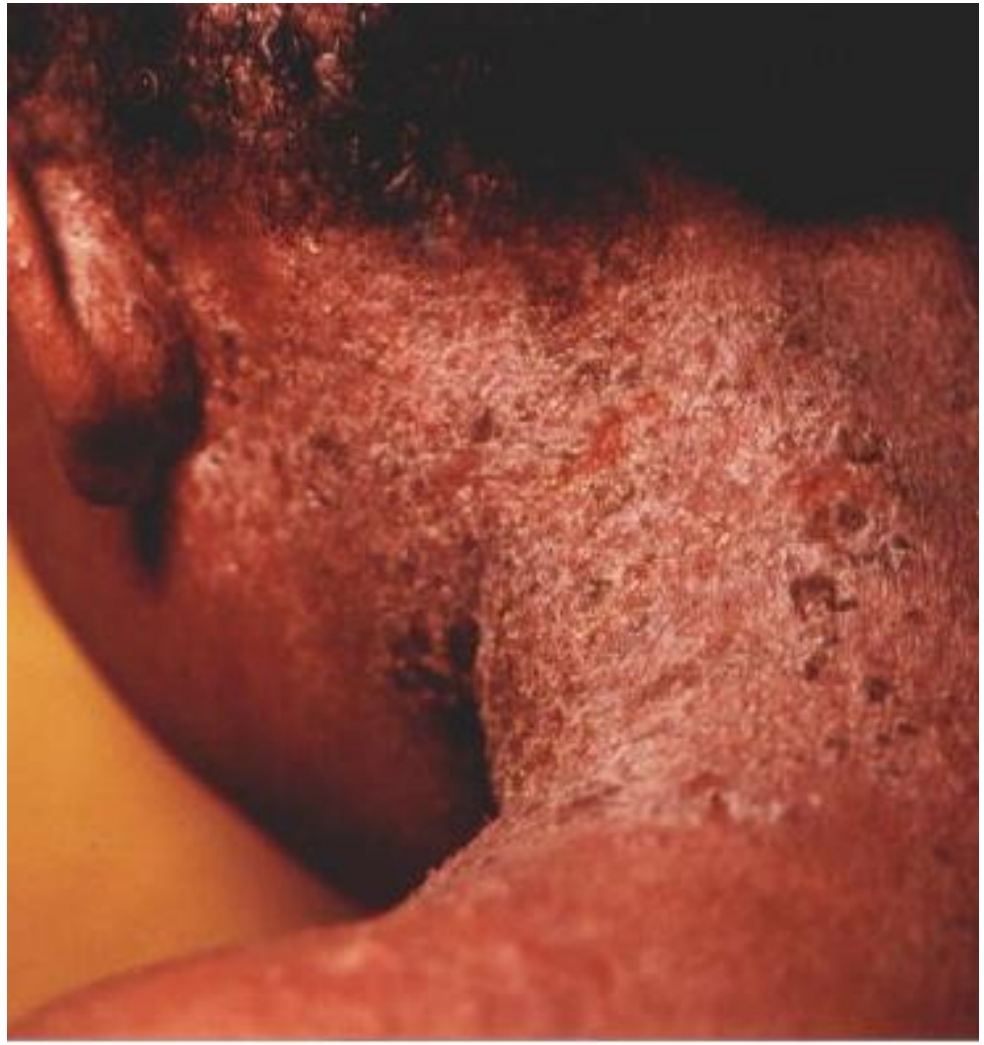
HTLV1 RELATED DISEASES

Myelopathy/tropical spastic paraparesis (HAM/TSP)

Uveitis

Adult T-cell lymphoma/leukemia, HTLV1-associated

HTLV1-associated infective dermatitis (IDH)

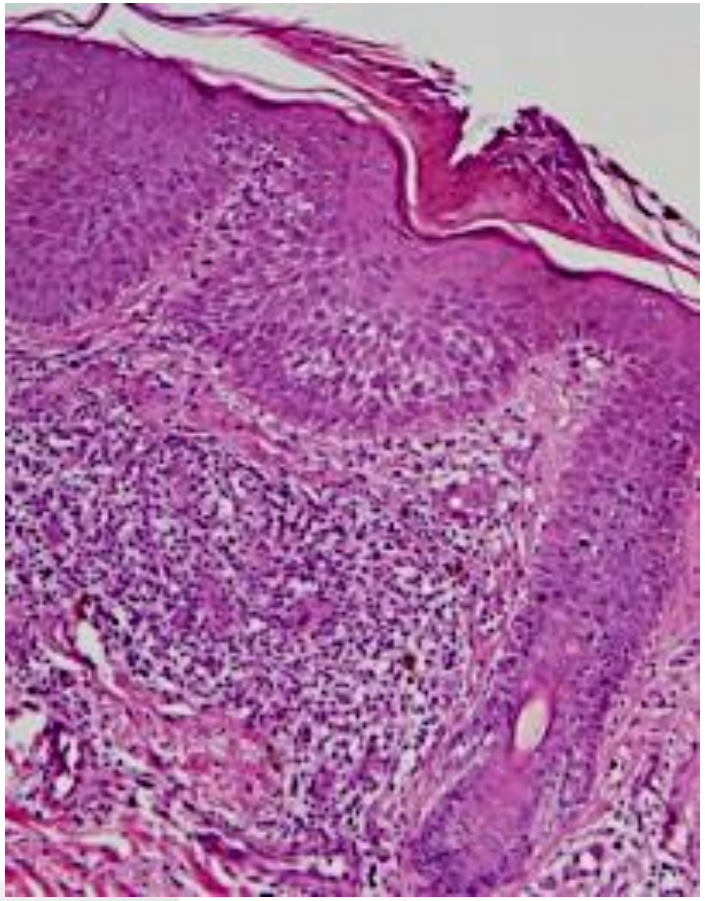


HTLV1 ASSOCIATED INFECTIVE DERMATITES

- It is a chronic and severe form of childhood eczema characterized by an exudative and infected dermatitis, involving the scalp and retroauricular regions
- First described in Jamaica in 1966 by Sweet.
- In 1990 it was related to HTLV-1.
- HTLV1 infection related to vertical transmission in most cases
- Associated myelopathy/tropical spastic paraparesis (30% to 50% of the cases)
- **Progression to Adult T cell Leukemia/Lymphoma in rare cases** *de Oliveira et. al. Clin Infect Dis. 2012. doi: 10.1093/cid/cis273*

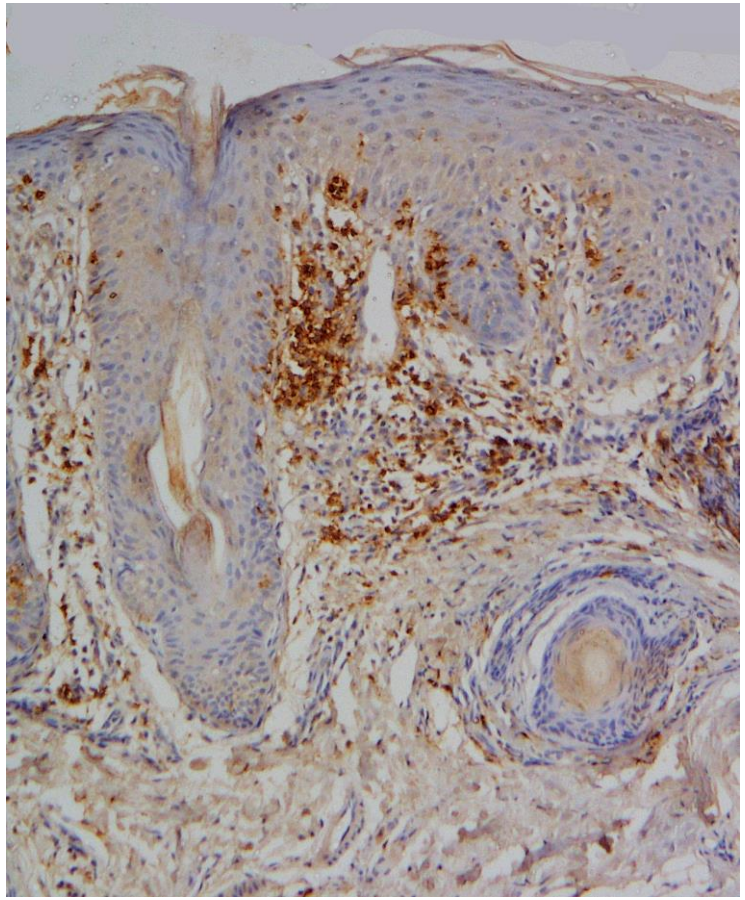
HISTOPATHOLOGICAL AND IMMUNOHISTOLOGICAL FINDINGS (HTLV1-ASSOCIATED INFECTIVE DERMATITES)

Acanthosis, parakeratosis and spongiosis with a mild inflammatory infiltrate

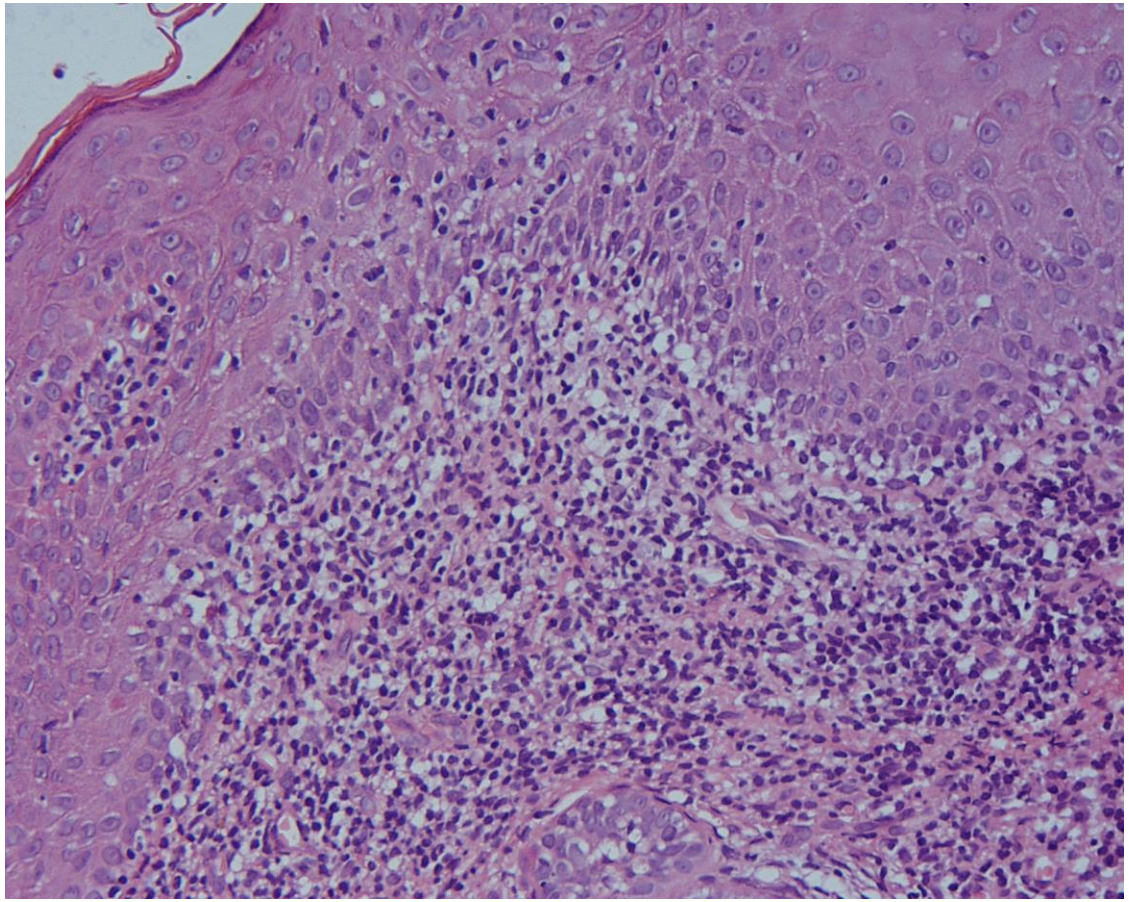


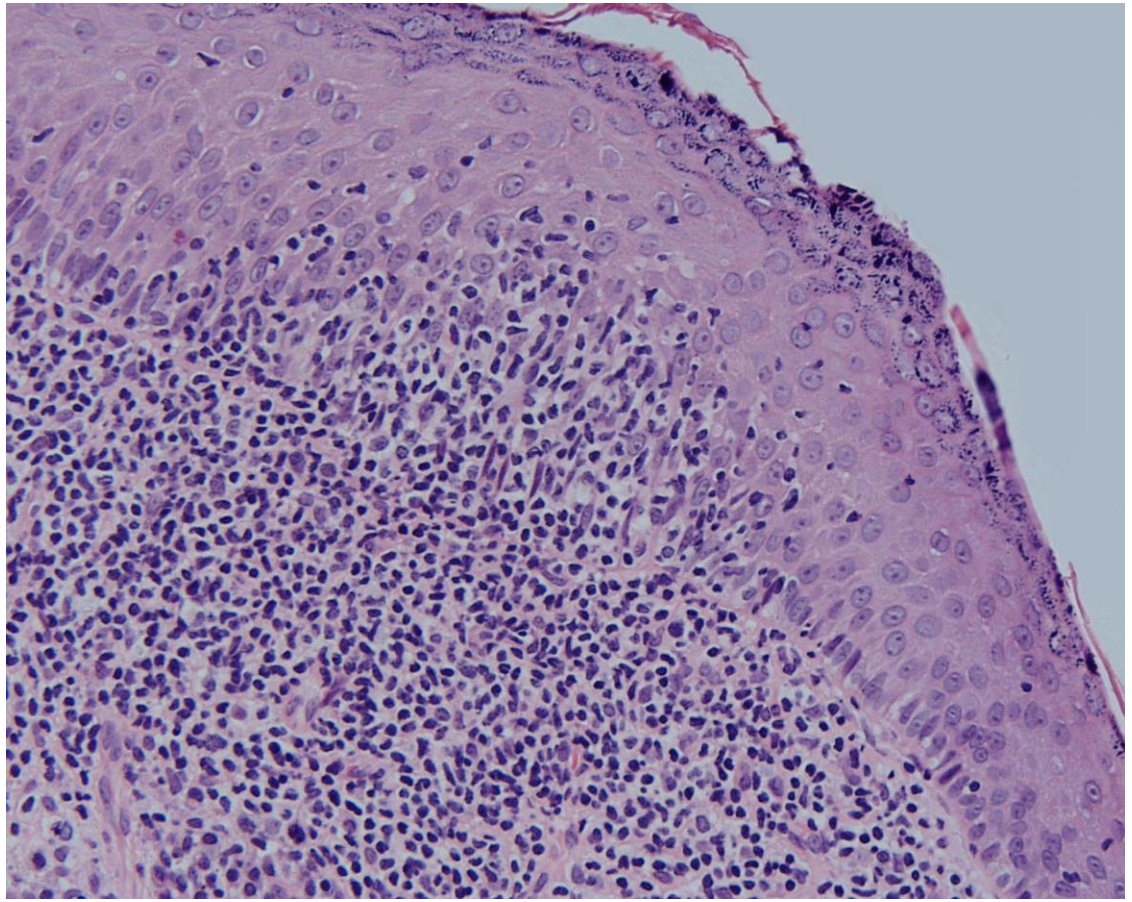
Bittencourt et. al., Eur J Dermatol. 2005 Jan-Feb;15(1):26-30

T cells, CD3+; **CD8+,** CD4-; few Granz B+



HISTOPATHOLOGICAL FINDINGS IN DIH: LYMPHOCYTIC EPIDERMOTROPISM (50% OF THE CASES) (20% MIMICKING MYCOSIS FUNGOIDES)



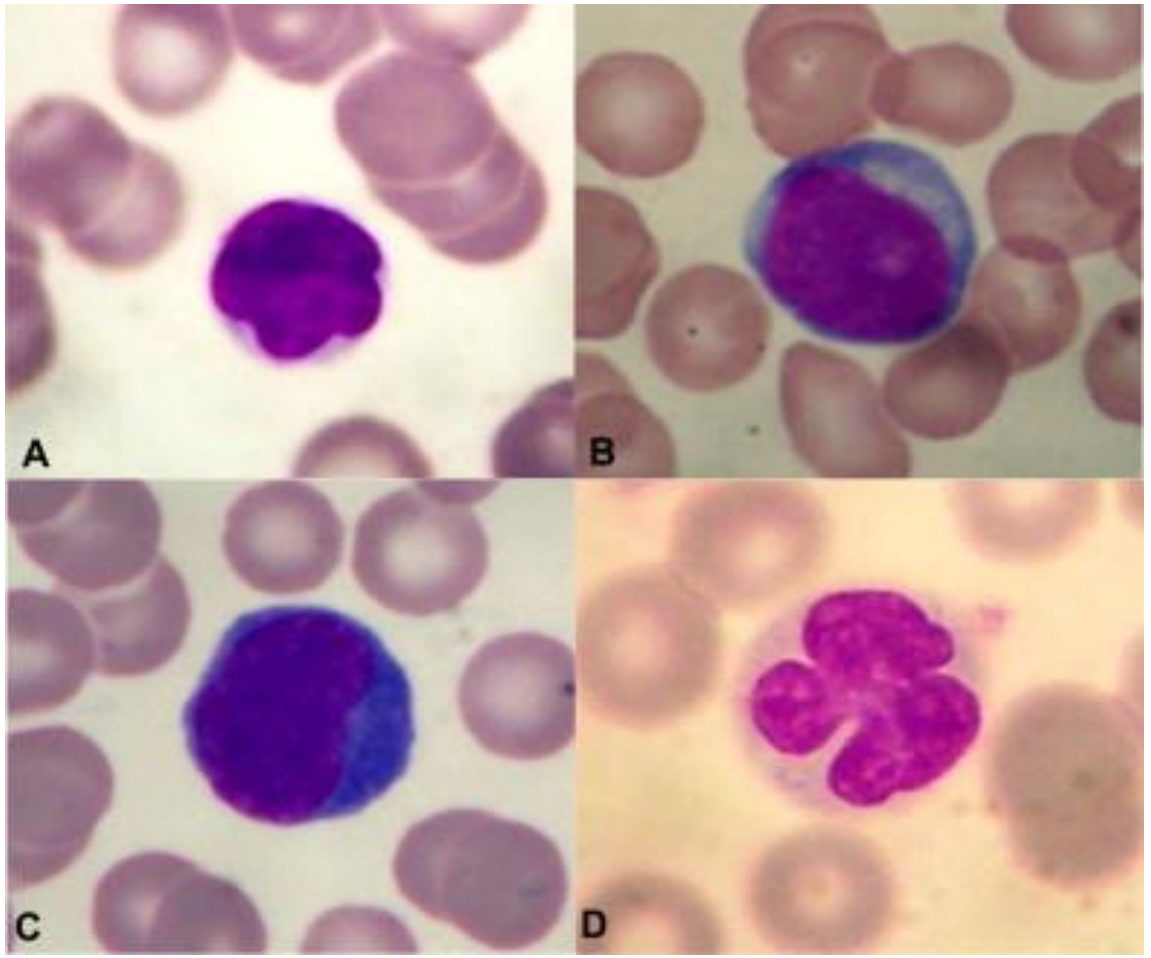


- *Bittencourt et. al., Eur J Dermatol. 2005 Jan-Feb;15(1):26-30*

HTLV1 ASSOCIATED INFECTIVE DERMATITES AND ATYPICAL CELLS

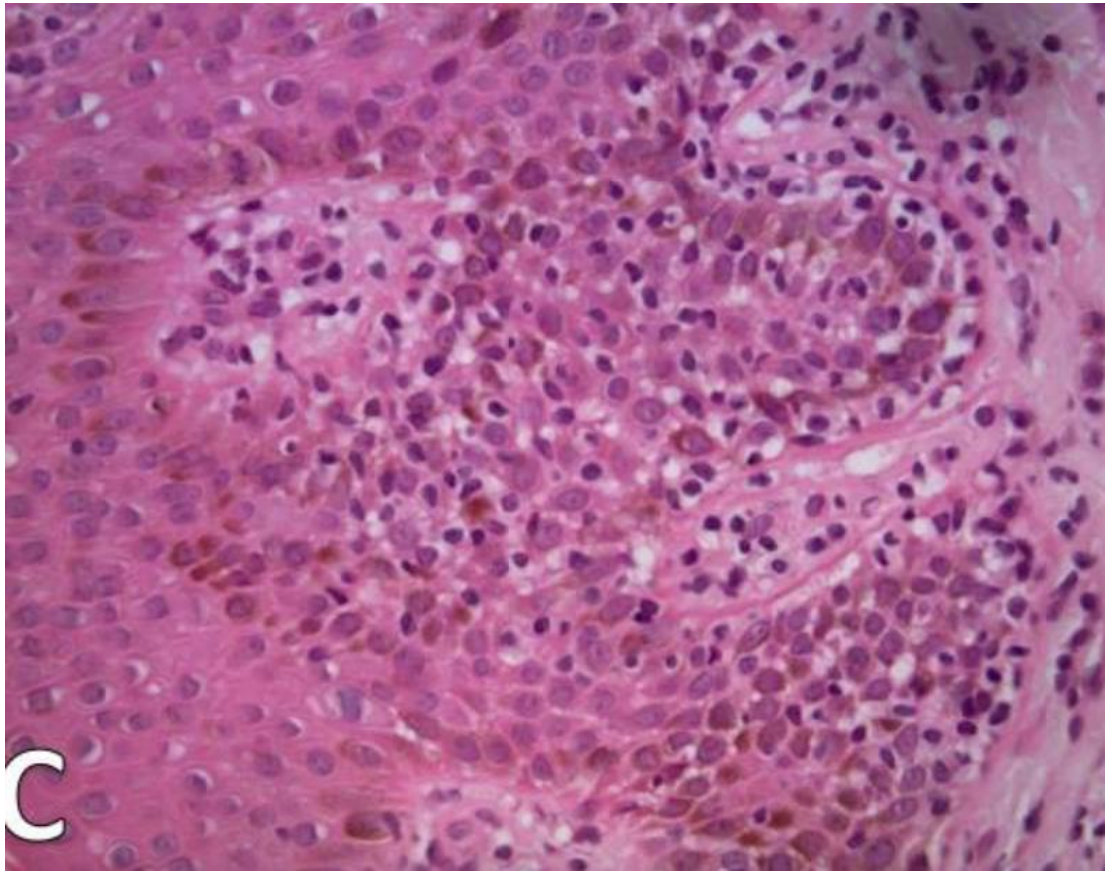
Abnormal Lymphocytes in the peripheral blood smears in nine of 30 patients (30%)

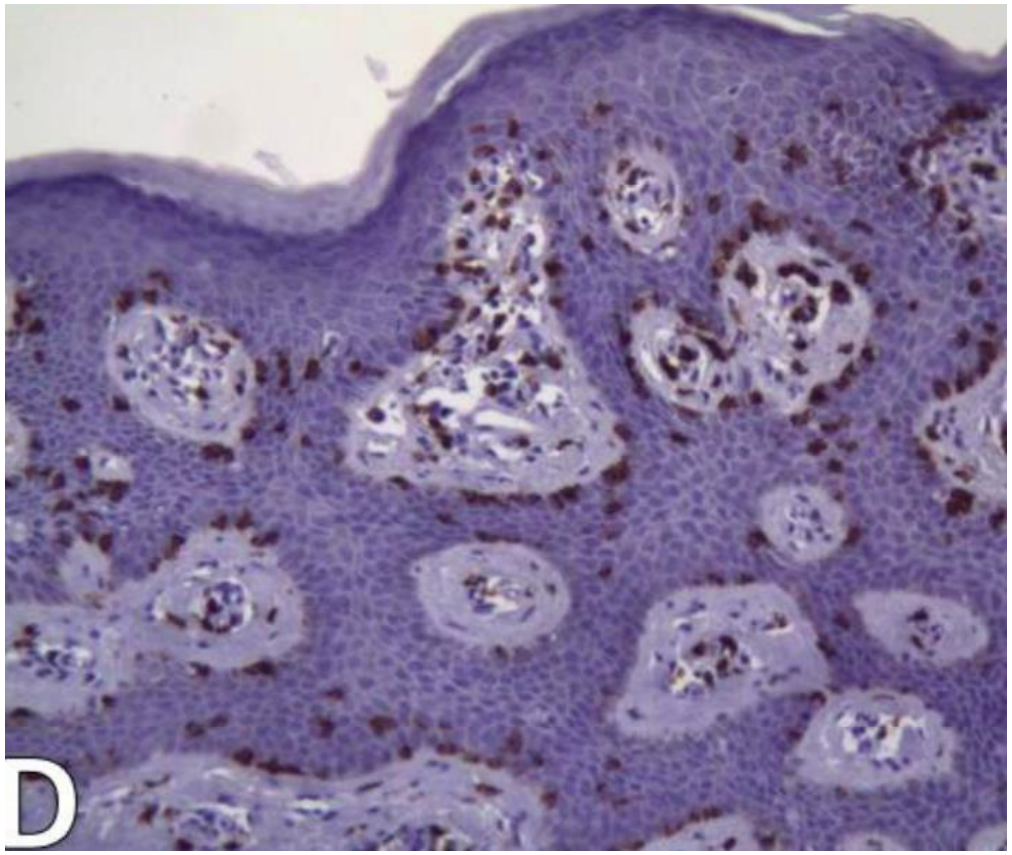
Flower cells in 5 of 30 patients (16%) with a tendency to greater proviral load



Oliveira et. al. J Clin Virol. 2010 Aug;48(4):288-90. doi: 10.1016/j.jcv.2010.05.005.)

INFECTIVE DERMATITIS ASSOCIATED WITH HTLV-I IN ADULT Souza LS et. al.: PLoS Negl Trop Dis. 2020 Apr 24;14(4):e0008241. doi: 10.1371/journal.pntd.0008241)





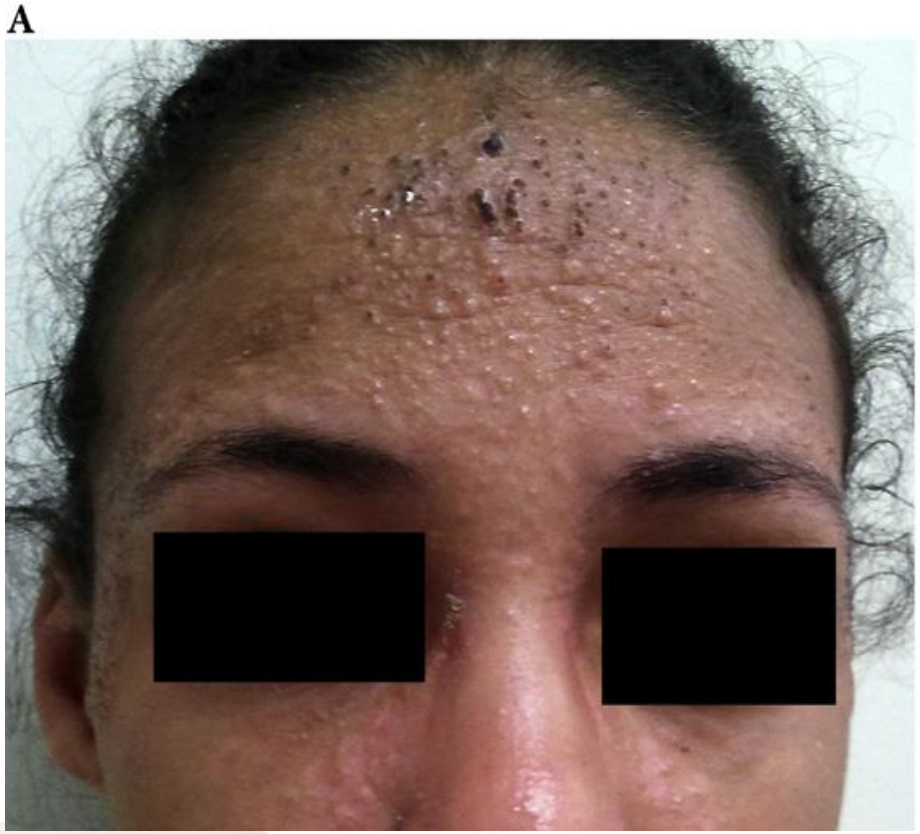
Salomón M et. al:Folia Dermatológica Peruana. 2001;12(1): 41 ; Olivares et.al.: Dermatologia Argentina 2009;15(1): 49–53; ***Maragno L et. al. 2009;48(7): 723–30. 10.1111/j.1365-4632.2009.04008; Okajima R et.al.: Int J Dermatol. 2013;52(1): 63–8. 10.1111/j.1365-4632.2012.05606***

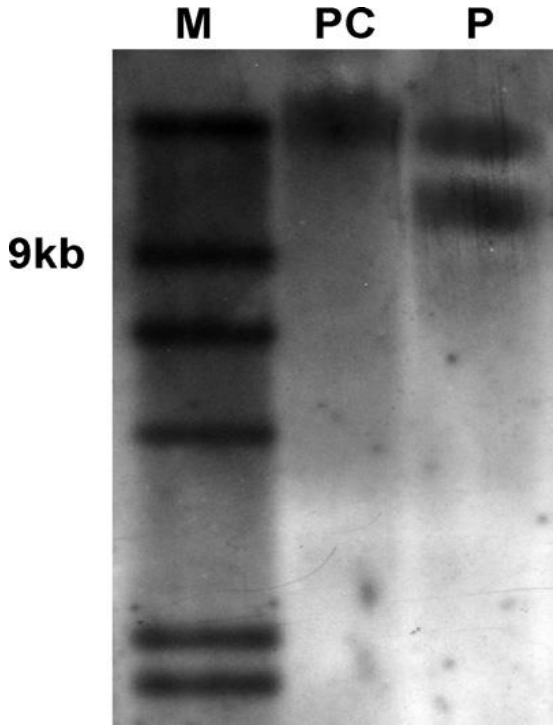
PROGRESSION OF INFECTIVE DERMATITIS ASSOCIATED WITH HTLV-1 TO ADULT T-CELL LEUKEMIA/LYMPHOMA

Oliveira et al, J. Clin. Virol, 2013

19-year-old patient developed an acute form of adult T-cell leukemia/lymphoma

History of infective dermatitis (IDH) since she was three years old

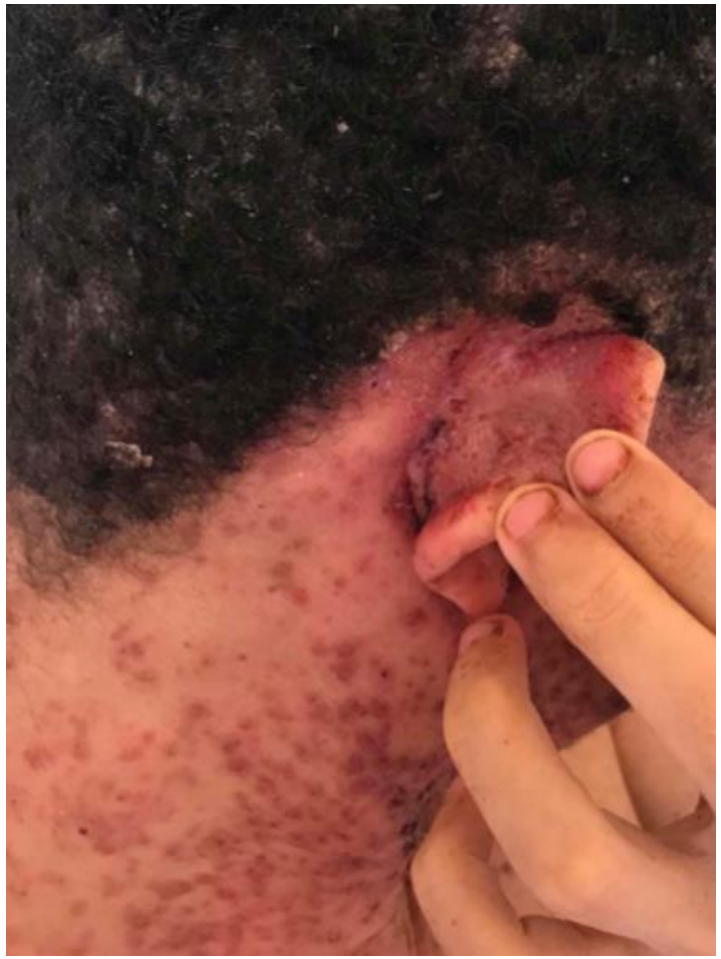


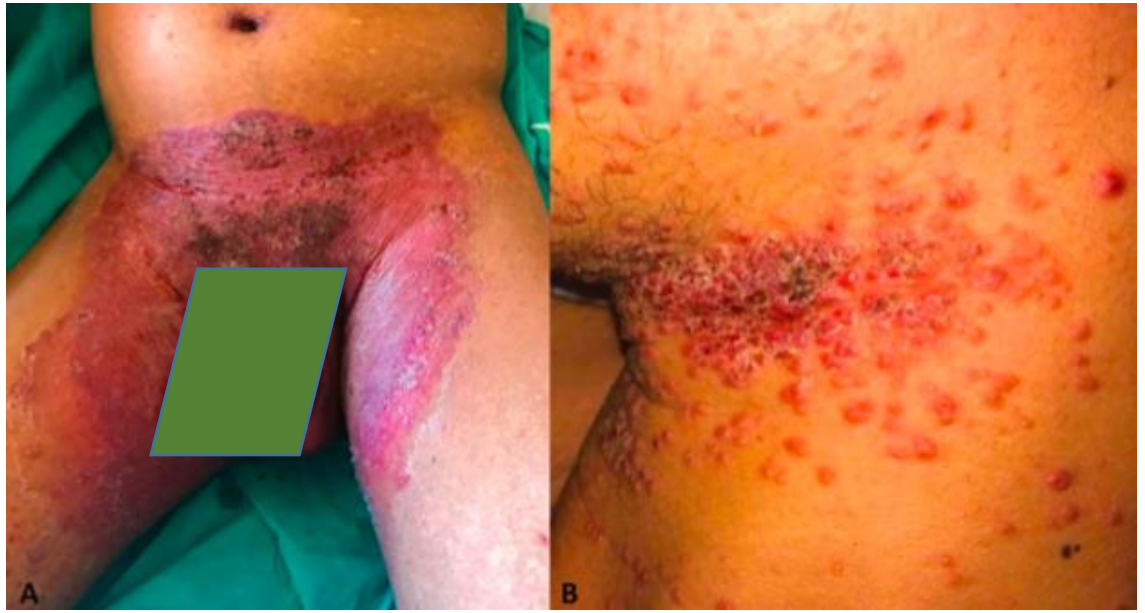


Double integration band southern blot
PC control/ P= patient

PROGRESSION OF INFECTIVE DERMATITIS ASSOCIATED WITH HTLV-1 TO ADULT T-CELL LEUKEMIA/LYMPHOMA

22-year-old man who had IDH since childhood and developed ATLL 18 months ago – Type Chronic





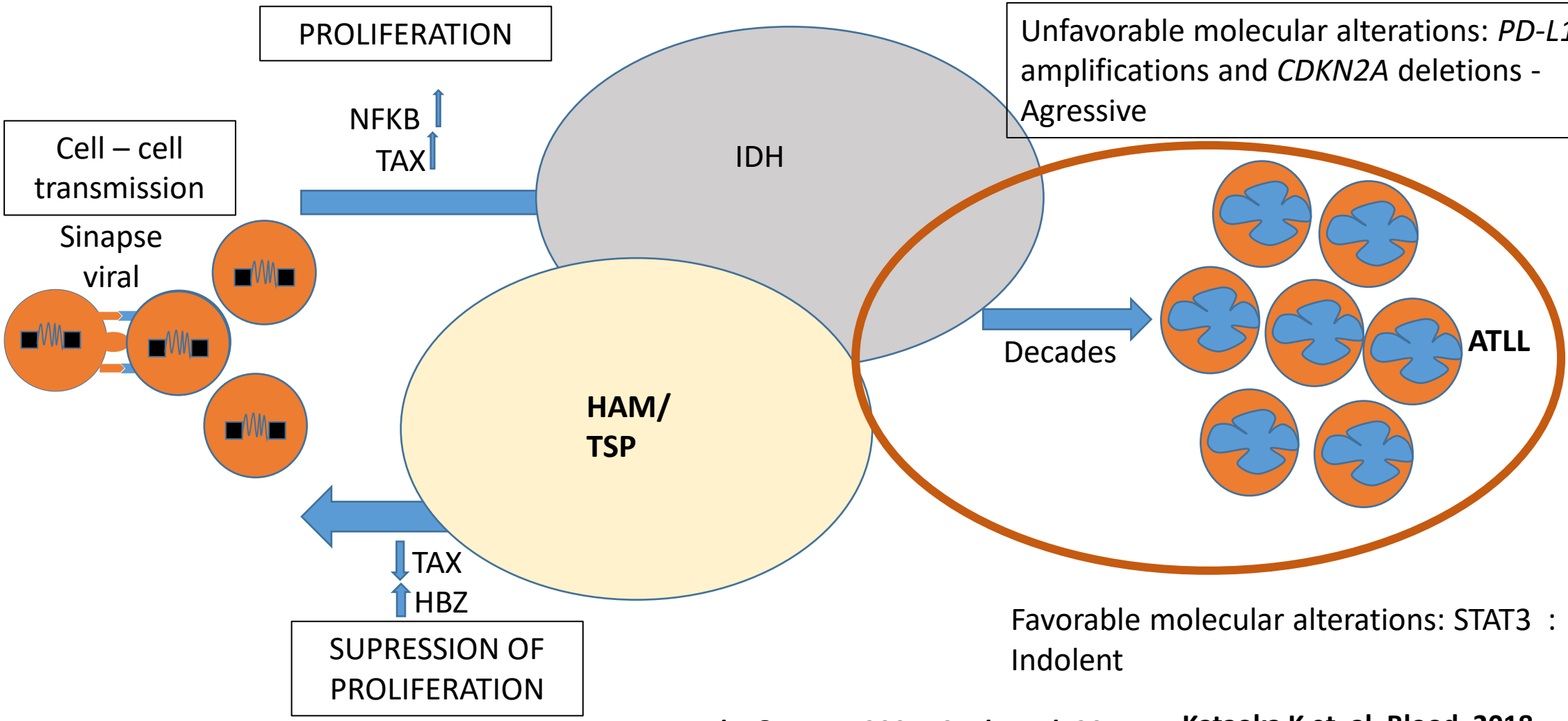
The lymphoma lesions were superimposed on previously existing IDH lesions

Rosa et.al.: Am J Dermatopathol Volume 44, Number 5, May 2022

PROGRESSION OF INFECTIVE DERMATITIS ASSOCIATED WITH HTLV-1 TO ADULT T-CELL LEUKEMIA/LYMPHOMA *(ROSA BL ET.AL. AM J DERMATOPATHOL. 2022 MAY 1;44(5):368-371. DOI: 10.1097/DAD.0000000000002044.*

Cases	Age* /sex	Age at IDH onset	Sites of IDH	Age at ATL onset	ATL skin lesions	ATL sites	ATL type
1.Hanchard B et al, 1991	20y/M	3y	Face and Scalp	20y	Widespread scaly macular rush	Disseminated, lymph node, liver, spleen	Acute
2.Gonçalves et al, 2000	28 y/F	childhood	Scalp and RA	28 y	Plaque	RA	smoldering
3.Farre et al. 2008	12 y/F	3 y	Disseminated including scalp, nostrils and RA	16 y	Papules	Back	Smoldering
4.Oliveira et al, 2013	19 y/F	3 y	Scalp, RA, face and neck	18 y	Papules, macules	Disseminated	Acute
5. Rosa et.al, 2022	22y/M	1 y	Scalp, RA, forehead, axillae, antecubital and popliteal fossae and umbilicus	20 y	Plaques. Disseminated papules, and vesicles	Scalp, RA, neck, arms, back, axillae, umbilicus, genitalia, hypogastrium, groin and buttocks	Chronic

PATOGENESIS OF HTLV1 INFECTION



Matsuoka & Jeang,2007; Cook et al, 2017

Kataoka K et. al. Blood. 2018

ADULT T-CELL LEUKEMIA/LYMPHOMA

Mature T-cell leukemia/lymphoma associated with human T-cell lymphotropic virus type 1 (HTLV1)

Serology positive for HTLV-1 (ELISA), confirmed by Western blot or polymerase chain reaction (PCR).

Median age at diagnosis is **49 years (Brazil);** 40 y (Jamaica); 60 y (Japan)

Malpica L et. al JCO Glob Oncol. 2021 Jul;7:1151-1166. doi: 10.1200/GO.21.00084. (253 cases: 1995-1019)

Oliveira PD et. al: PLoS Negl Trop Dis. 2022 Oct 19;16(10):e0010807. doi: 10.1371/journal.pntd.0010807 (1991-2017: 143 cases)

ADULT T-CELL LEUKEMIA/LYMPHOMA

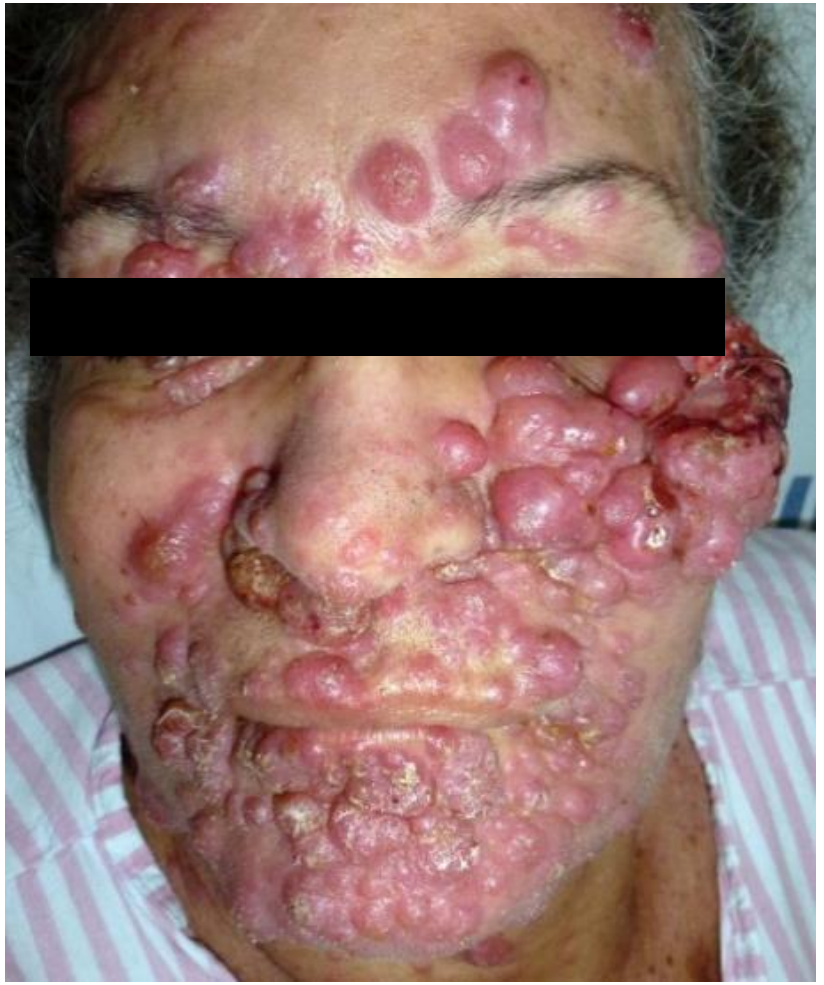
Four clinical subtypes: acute, chronic, lymphoma, and smoldering (by Shimoyama et.al, 1991) – OMS, 2022

Five clinical subtypes: + Primary cutaneous tumoral (PCT) * (Bittencourt, 2007)

History of DIH in the childhood in 26% of the cases in Bahia.

Cutaneous involvement in 67% of the cases

Bittencourt et al., 2007



Oliveira PD et. al: PLoS Negl Trop Dis. 2022 Oct 19;16(10):e0010807. doi: 10.1371/journal.pntd.0010807 (1991-2017: 143 cases)

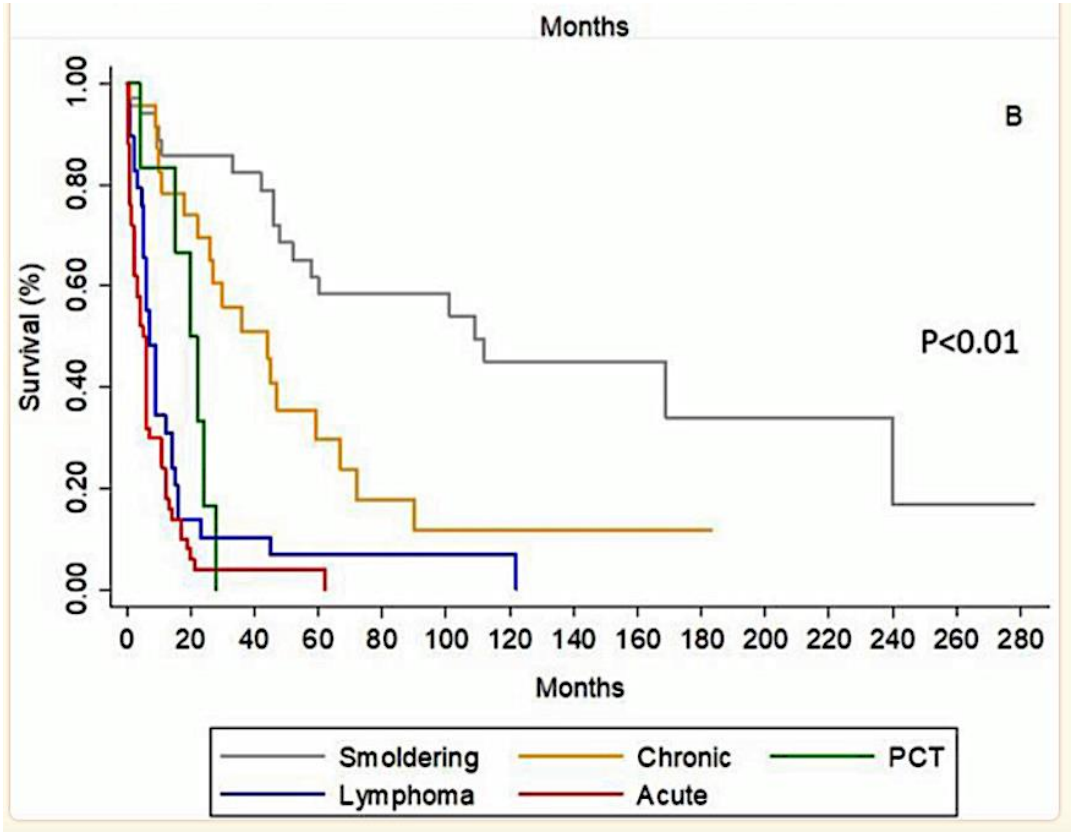
ADULT T-CELL LEUKEMIA/LYMPHOMA: CUTANEOUS PRIMARY TUMORAL (PTC) FORM

Distinct manifestation of ATLL, with cutaneous nodulotumoral lesions (originally included in the smoldering form)

Worse prognosis than the smoldering form

Should be treated as a Lymphoma

In the Revised Adult T-Cell Leukemia-Lymphoma International Consensus Meeting Report PCT it was named as extranodal primary cutaneous variant of the lymphoma type and was considered an aggressive ATLL type



Cook LB et. al.: Revised Adult T-Cell Leukemia-Lymphoma International Consensus Meeting Report. J Clin Oncol. 2019

Oliveira PD et. al, PLoS Negl Trop Dis. 2022 Oct 19;16(10):e0010807. doi: 10.1371/journal.pntd.0010807

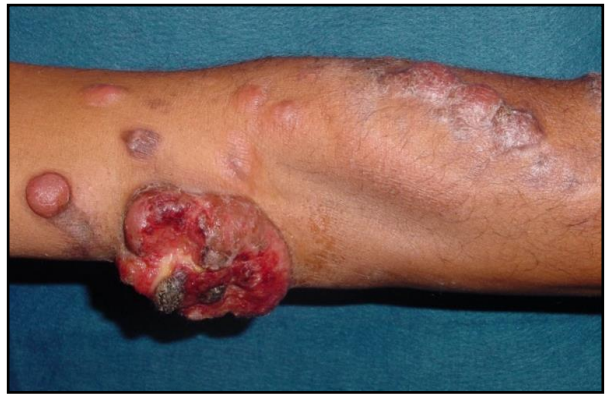
CLINICAL CLASSIFICATION OF ADULT T-CELL LEUKEMIA/LYMPHOMA (ATL). MODIFIED FROM THE SHIMOYAMA CLASSIFICATION: BITTENCOURT AL HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE-1 (HTLV-1) INFECTION IN DERMATOLOGY. IN. BONAMIGO, R RL, DORNELLES, S T (EDS.). SPRINGER INTERNATIONAL PUBLISHING, SWITZERLAND, 2018.

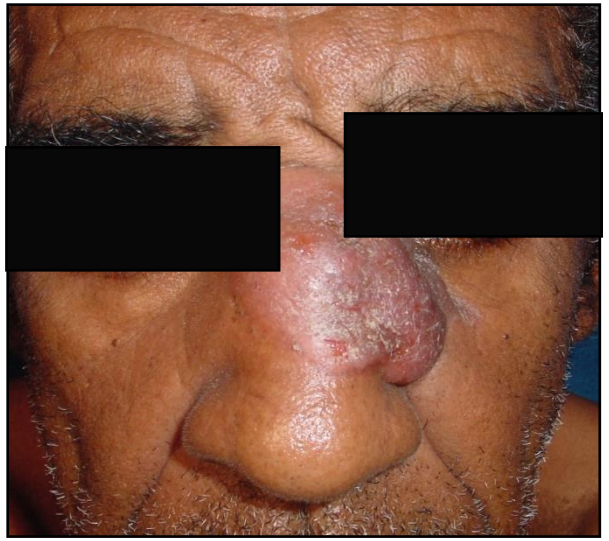
CCC	Lymphocytosis	Abnormal lymphocytes	LDH levels	Hypercal-cemia	Involvement of organs
Smoldering					
Primary cutaneous	Absent	< 5%	≤1.5 x N	Absent	Skin
Non-leukemic	Absent	< 5%	≤1.5 x N	Absent	Skin and lung or lung
Leukemic	Absent	≥ 5%	≤1.5 x N	Absent	Skin and/or lung
Leukemic	Absent	≥ 5%	≤1.5 x N	Absent	Without involvement
PCT	**Absent**	**< 5%**	**≤1.5 x N**	**Absent**	**Skin**
Chronic #	Present	Present	≤2 x N	Absent	Any organ except bone, GUT and CNS
Lymphoma	Absent	≤ %	Variable	May occur	Lymph node* and any other organ
Acute	Usually present	≥ 5%	>1.5 x N	May occur	Any organ

PCT: Primary cutaneous tumoral; #Subtyped into favorable and unfavorable according to the serum levels of albumin, urea nitrogen, and lactic dehydrogenase (LDH); N: normal value; GIT: gastrointestinal tract; CNS: central nervous system.
*Involvement of lymph node is a mandatory criterion.

ATLL - CUTANEOUS PRIMARY TUMORAL (PTC) FORM

- No leukocytosis
- No hypercalcemia
- No extracutaneous involvement
- Normal LDH (≤1,5x)
- Nodulotumoral skin lesions

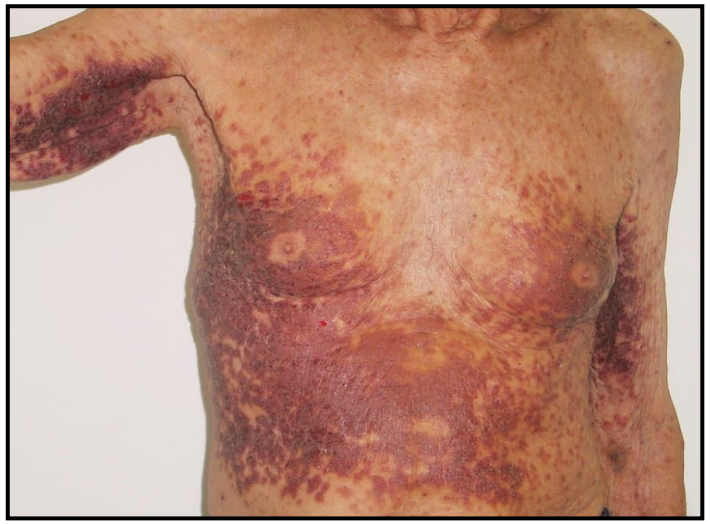


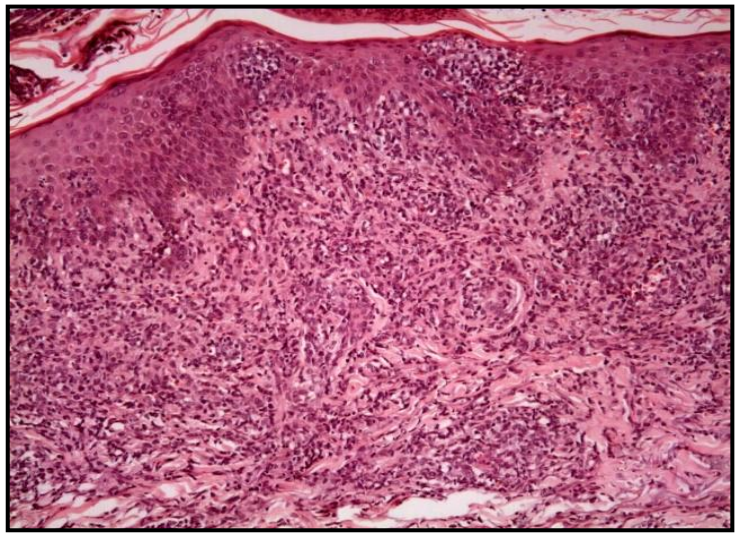


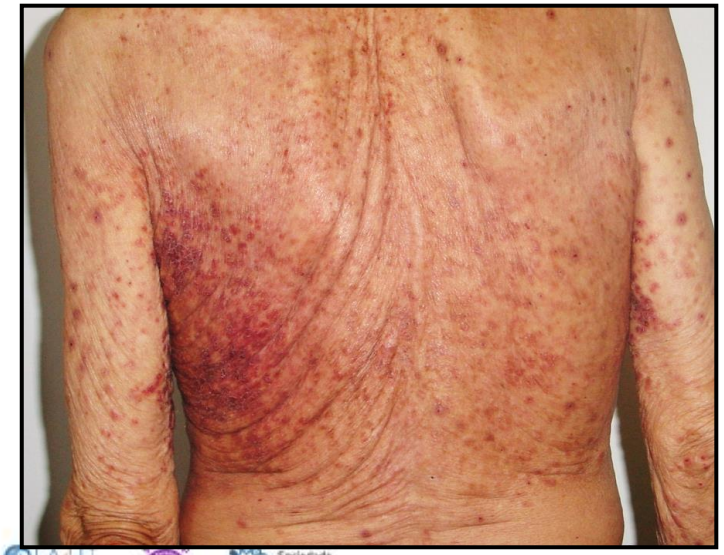
61 years old.
OS: 21 months

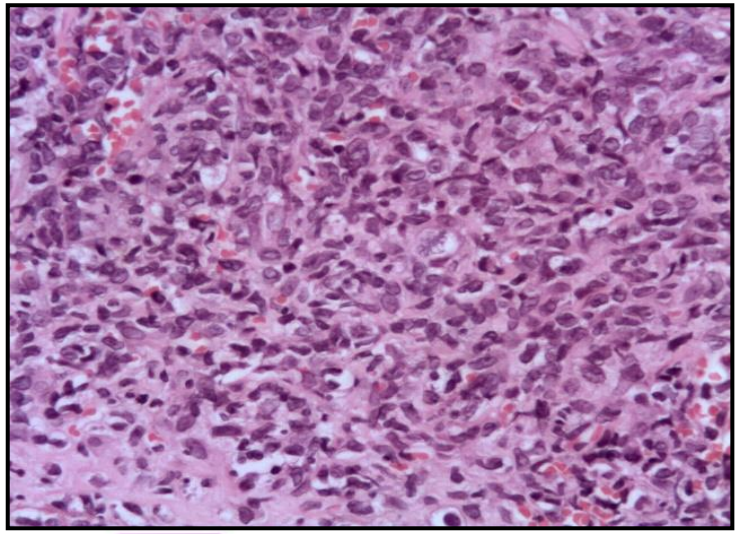
CUTANEOUS INVOLVEMENT IN ATLL (67% OF THE CASES, INDEPENDENT OF SUBTYPE)

ACUTE ATLL WITH PURPURIC LESIONS









Oliveira et al. Acta Oncol, 2011

CUTANEOUS T CELL LYMPHOMAS: FREQUENCY OF CUTANEOUS INVOVMENT IN ATLL, RELATION TO OTHER T/NK LYMPHOMAS

Bittencourt et al, 2013

CUTANEOUS T CELL LYMPHOMAS	
Mycosis fungoides	40,3%
ATLL	26,4%
PTCL, NOS	23,6%
Anaplastic large cell lymphomas	8,3%

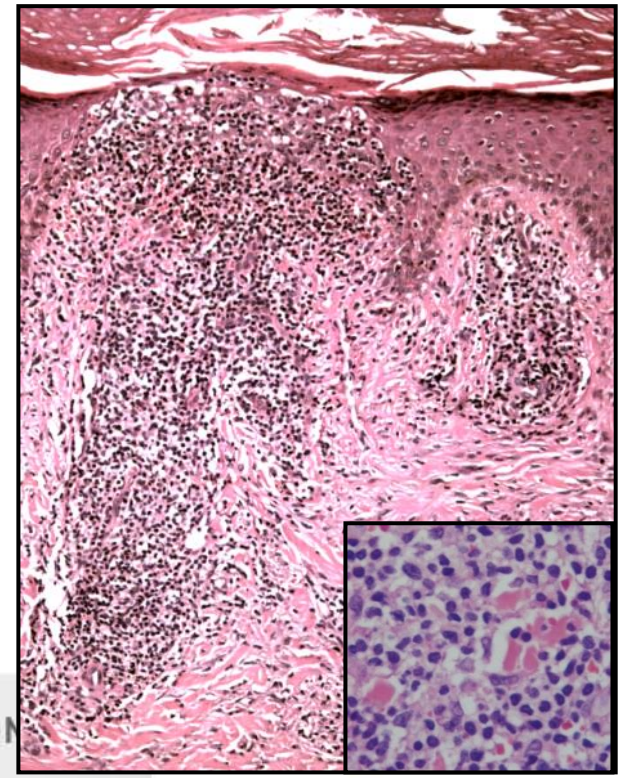
Em Lima, Peru, ATLL corresponde a 19,4% dos linfomas T primários da pele.

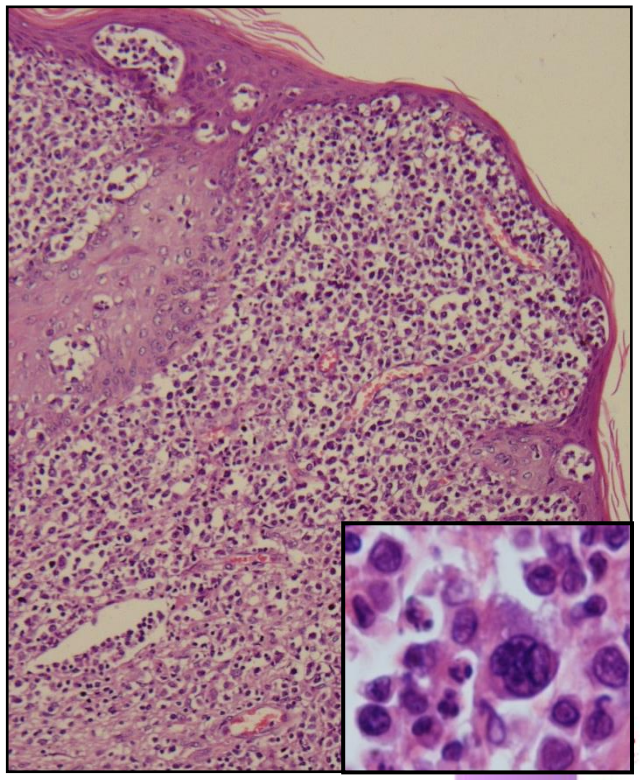
Garate et al 2008

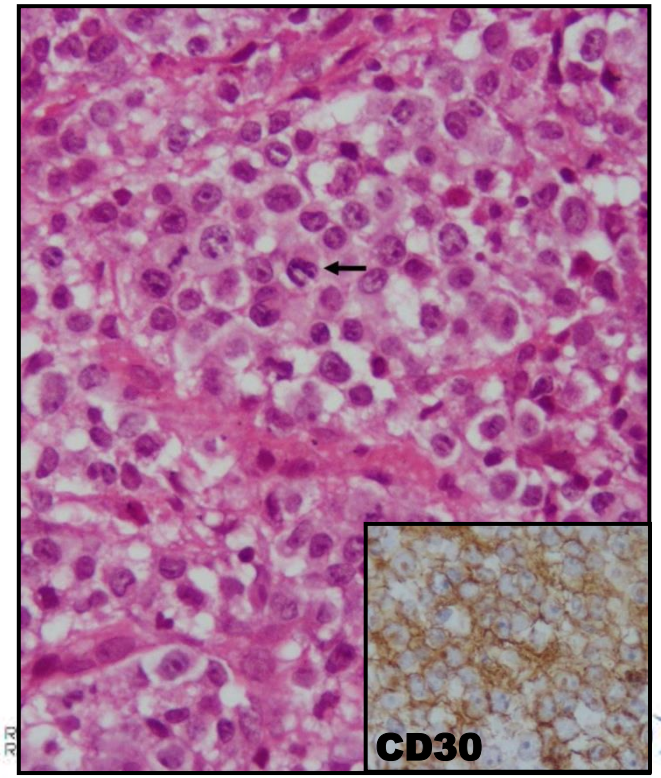
HISTOLOGICAL PATTERNS IN 77 CASES OF CUTANEOUS INVOLVEMENT IN ATLL

Bittencourt AL; Am J Clin Pathol.

Histological and immunohistological pattern	Number of cases
Peripheral T-cell lymphoma, NOS like	45
Mycosis fungoides like	29
Anaplastic large cell lymphoma (ALK-) like	3

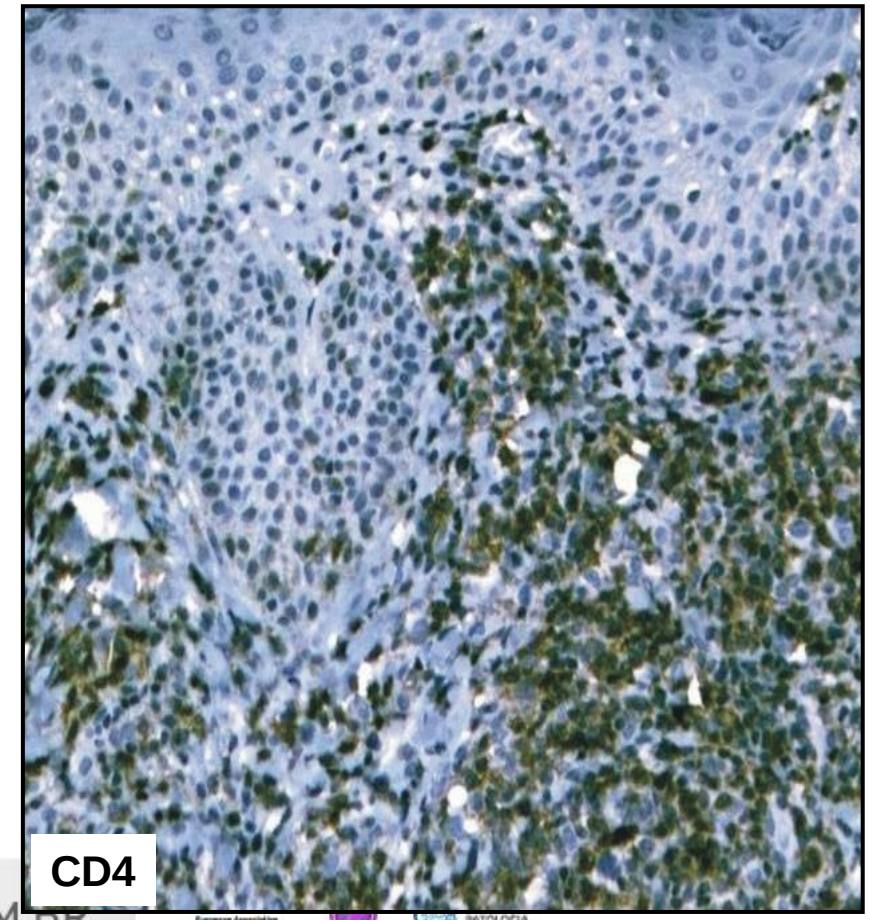


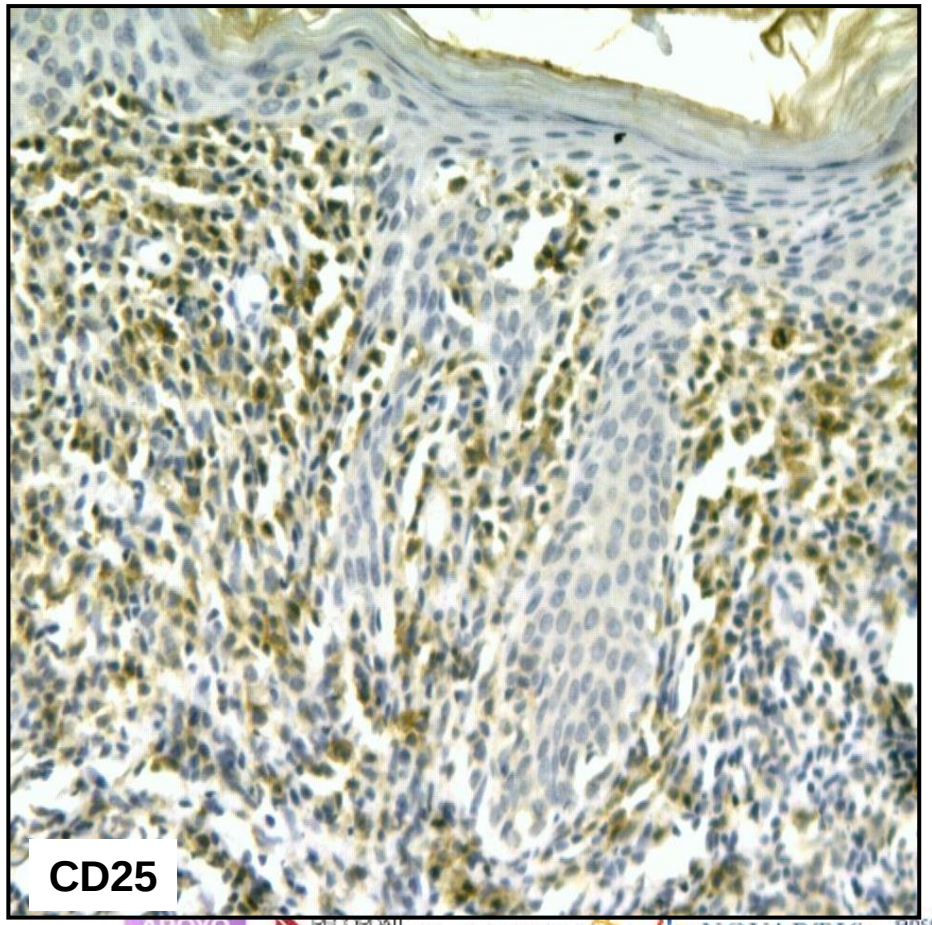




ADULT T-CELL LEUKEMIA/LYMPHOMA: IMMUNOPHENOTYPE

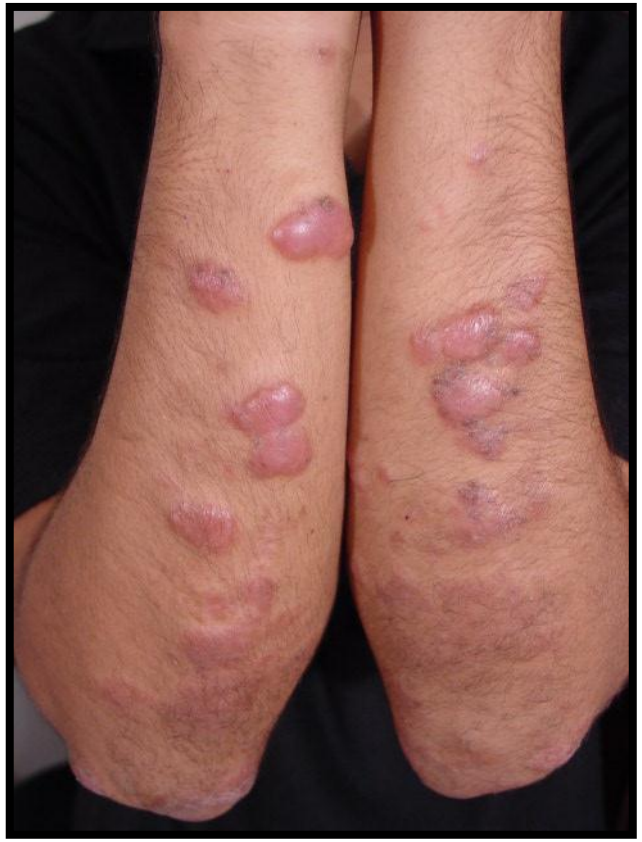
(CD3+, CD4+, CD5+, CD25+, CD7-, CD8-/+, CD30-/+, BCL2+; MUM1+/-)

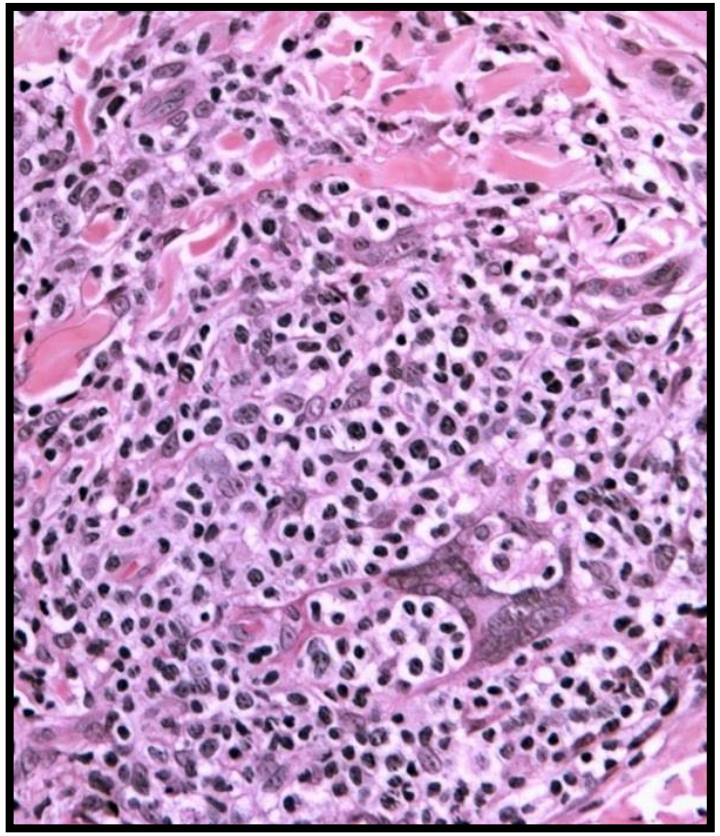


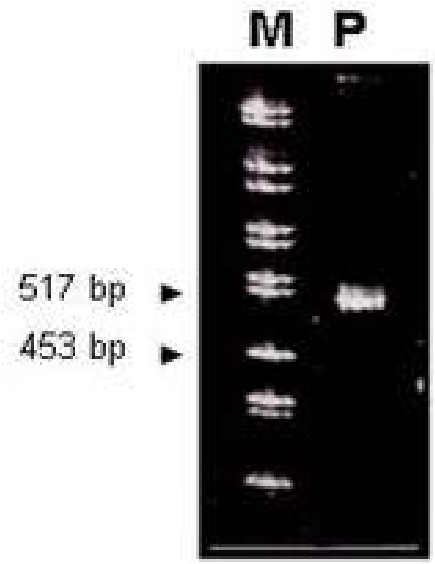


PEDIATRIC "ADULT" T-CELL LEUKEMIA/LYMPHOMA

9 year old - Chronic form – overall survival 22 years







Monoclonal integration of HTLV-1 (long-inverted PCR)

Lin BT et.al, 1997 Dec;121(12):1282-6. PMID: 9431320.

Oliveira et al., 2017

ATLL WITH HODGKIN-LIKE HISTOLOGIC FEATURES

Described by Ohshima et al, 1997 (18 cases (4 cases analyzed by single cell PCR):

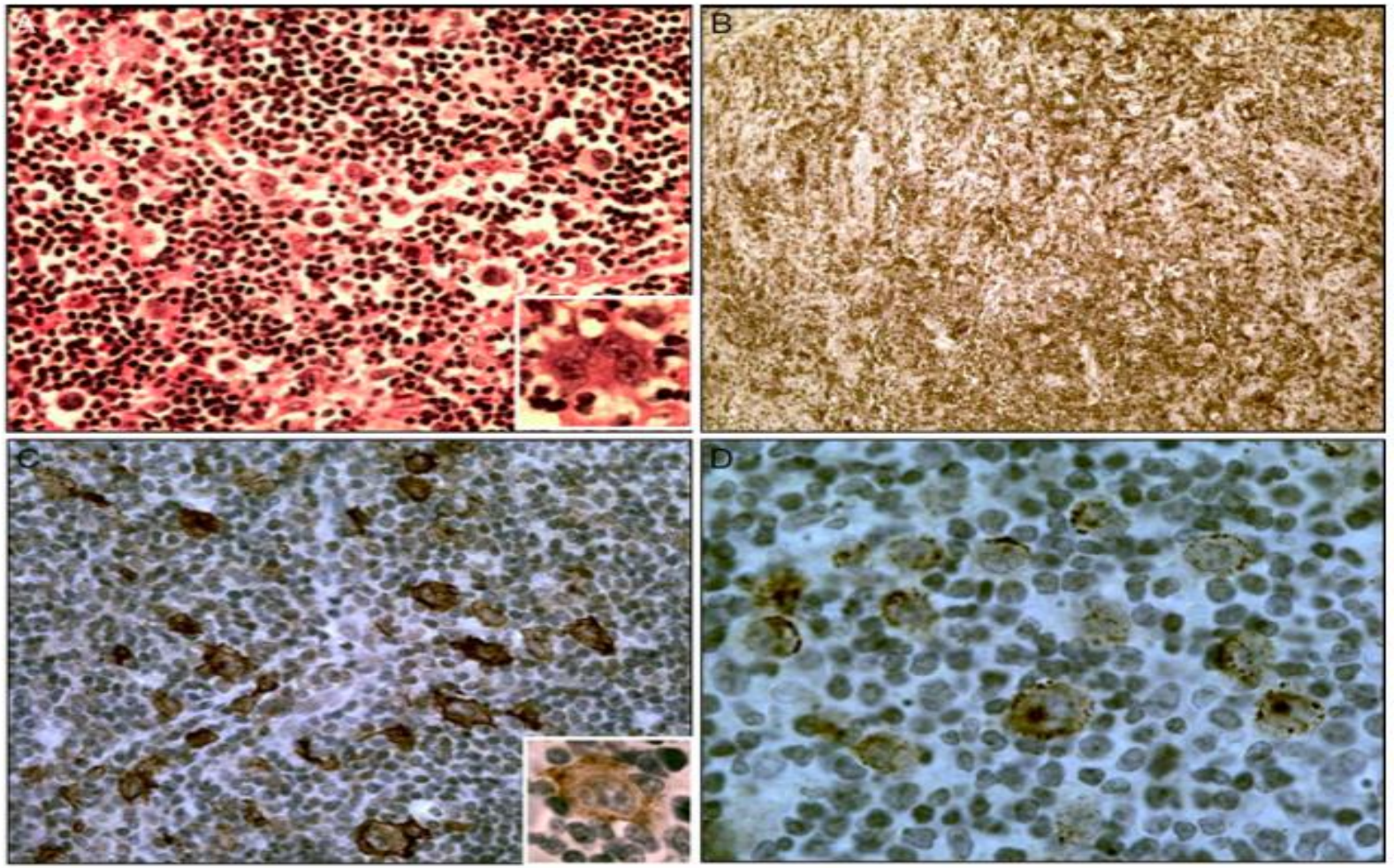
- RS like cells EBV+/EBV-; CD30+;CD15+; HTLV1 rare;
- Back ground lymphocytes: clonal HTLV-I-infected CD4+ T-lymphocytes and non-clonal non-HTLV-I-infected giant cells in incipient ATLL with Hodgkin-like histologic features. Int J Cancer. 1997;72:592–8.

Recently, Karube K et.al, Blood Adv. 2021 Jan 12;5(1):198-206.

- ATLL with HTLV-1–infected HRS-like cells is a new pathological variant of ATLL, **distinct from conventional Hodgkin-like variant of ATLL**.
- Diffuse HBZ-ISH positivity and negativity for PAX5 and EBV are key features distinguishing this variant from other morphological mimics.

HODGKIN-LIKE ADULT T-CELL LEUKEMIA/LYMPHOMA

Bittencourt et. Al. 2017



Hodgkin-Like cells: CD30+; CD20+; EBV+; CD15-

The background T cells were atypical and CD3+;CD4+;CD5+;CD5+; CD7-

LINFOMA DE HODGKIN SÍMILE EM PACIENTES HTLV-1 POSITIVOS

Autor, ano	N/age	RS-cell phenotype	Lymphocytes phenotype	OS
Picard F, 1990	1/ f 38y	CD15+, CD45	ND (citomet.)	8 months
Hayashi-T, 1995	1/ND	CD30+, CD15+, **EBV+**	CD3+, CD4+, **CD7-**	ND
Sadhira, 1998	2 cases*/ 48a, 50a	CD30+ CD15+ **EBV+**	ND	alive* 2 years
Venkataraman-G, 2011	1/52y	CD30+ CD15+ **EBV+**	CD3+; CD+ **CD25+; CD7-** CD20 & EBV+	CR pos QT
Bittencourt, AL, 2017	**1/f 46y**	**CD30, EBV+, CD79a**	**CD3+; CD4+ CD25+; CD7dim**	**2 anos**

CONCLUSIONS

ATLL may mimic PTCL, ALCL (ALK-) and MF, clinically, histologically and immunophenotypically

In HTLV1-endemic areas, HTLV 1 serology should be recommended in all cases of mature T-cell lymphoma, regardless of subtype, even in children.

Should we consider serology for Hodgkin's lymphomas with a negative CD7 cell background (?)

Clinical-laboratory elements such as calcium levels, LDH, organ damage, leukogram are indispensable for categorization of the clinical form, with an impact on survival/prognosis

The Primary cutaneous tumoral form has worse prognosis than Smoldering and should be considered as a distinct clinical form.

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