L'IDENTIKIT DEI LINFOCITI CIRCOLANTI

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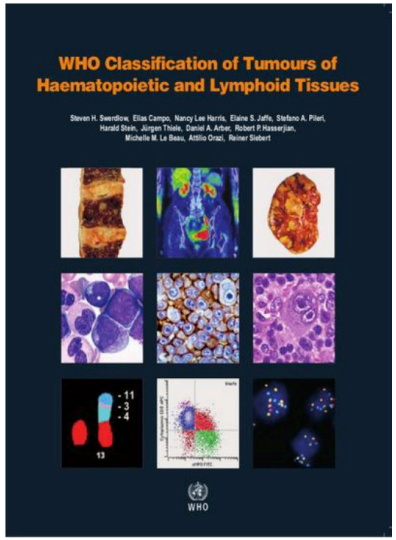
- U.O.C. di Dermatologia e Università degli Studi di Milano

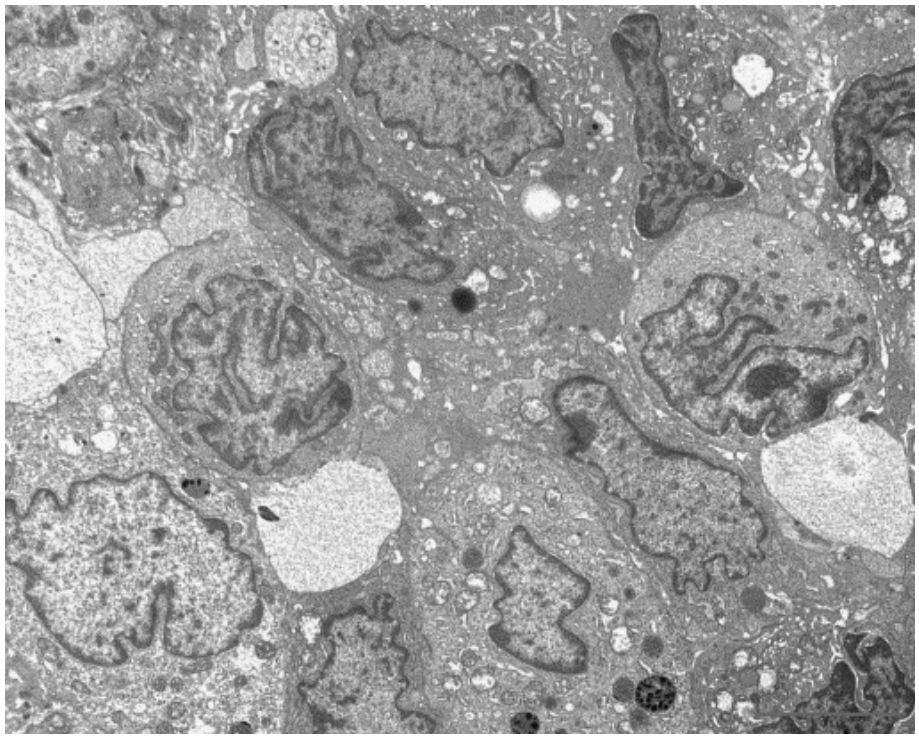
Updated 4° edition of WHO classification



WHO-EORTC Classification 2018	Frequency, %*	5-y DSS, %*
CTCL		
MF	39	88
MF variants		
Folliculotropic MF	5	75
Pagetoid reticulosis	<1	100
Granulomatous slack skin	<1	100
SS	2	36
Adult T-cell leukemia/lymphoma	<1	NDA
Primary cutaneous CD30⁺ LPDs		
C-ALCL	8	95
LyP	12	99
Subcutaneous panniculitis-like T-cell lymphoma	1	87
Extranodal NK/T-cell lymphoma, nasal type	<1	16
Chronic active EBV infection	<1	NDA
Primary cutaneous peripheral T-cell lymphoma, rare subtypes		
Primary cutaneous γ/δ T-cell lymphoma	<1	11
CD8⁺ AECTCL (provisional)	<1	31
Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder (provisional)	6	100
Primary cutaneous acral CD8⁺ T-cell lymphoma (provisional)	<1	100
Primary cutaneous peripheral T-cell lymphoma, NOS	2	15

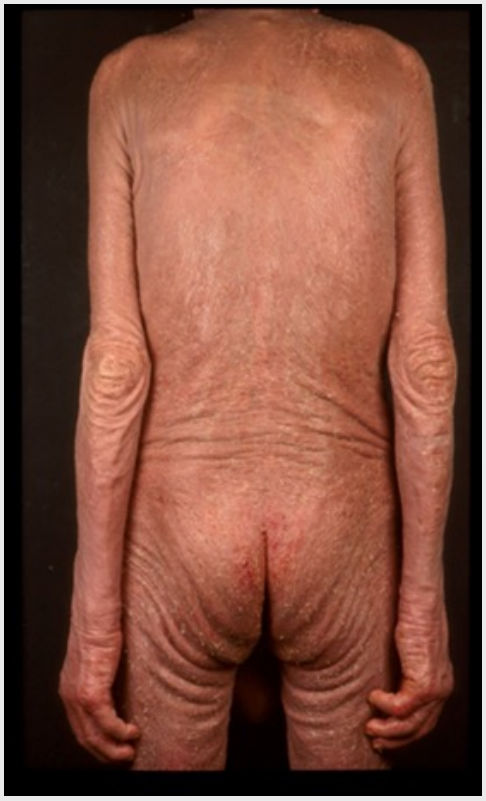
MYCOSIS FUNGOIDES

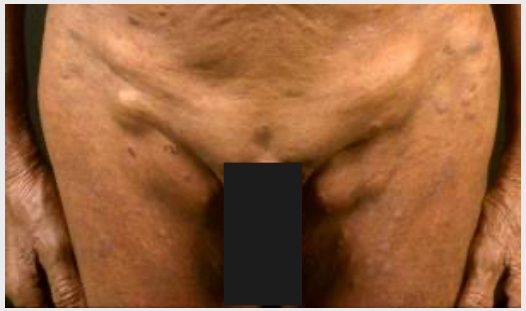
- Classic MF (Alibert-Bazin type) is the most frequent clinical subtype of CTCL
- A neoplastic clonal epidermotropic proliferation of small/medium-sized cerebriform effector memory T-cell
- Median age at diagnosis: 55 yrs (5°-6° decades of life)
- Male to female ratio: 1.6-2.0/1

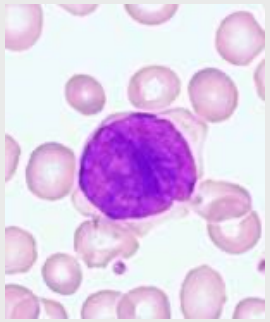


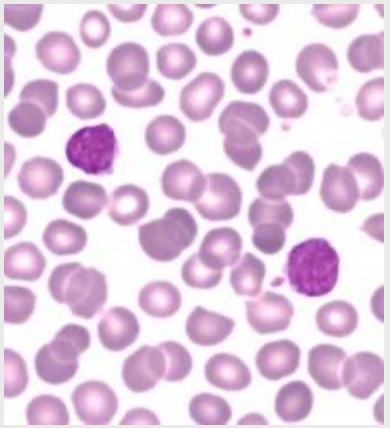
Cerebriform cells

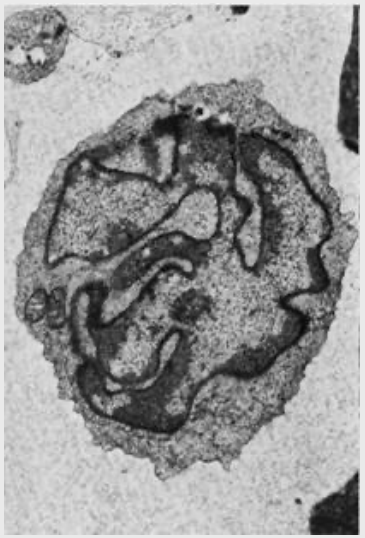
SINDROME DI SEZARY





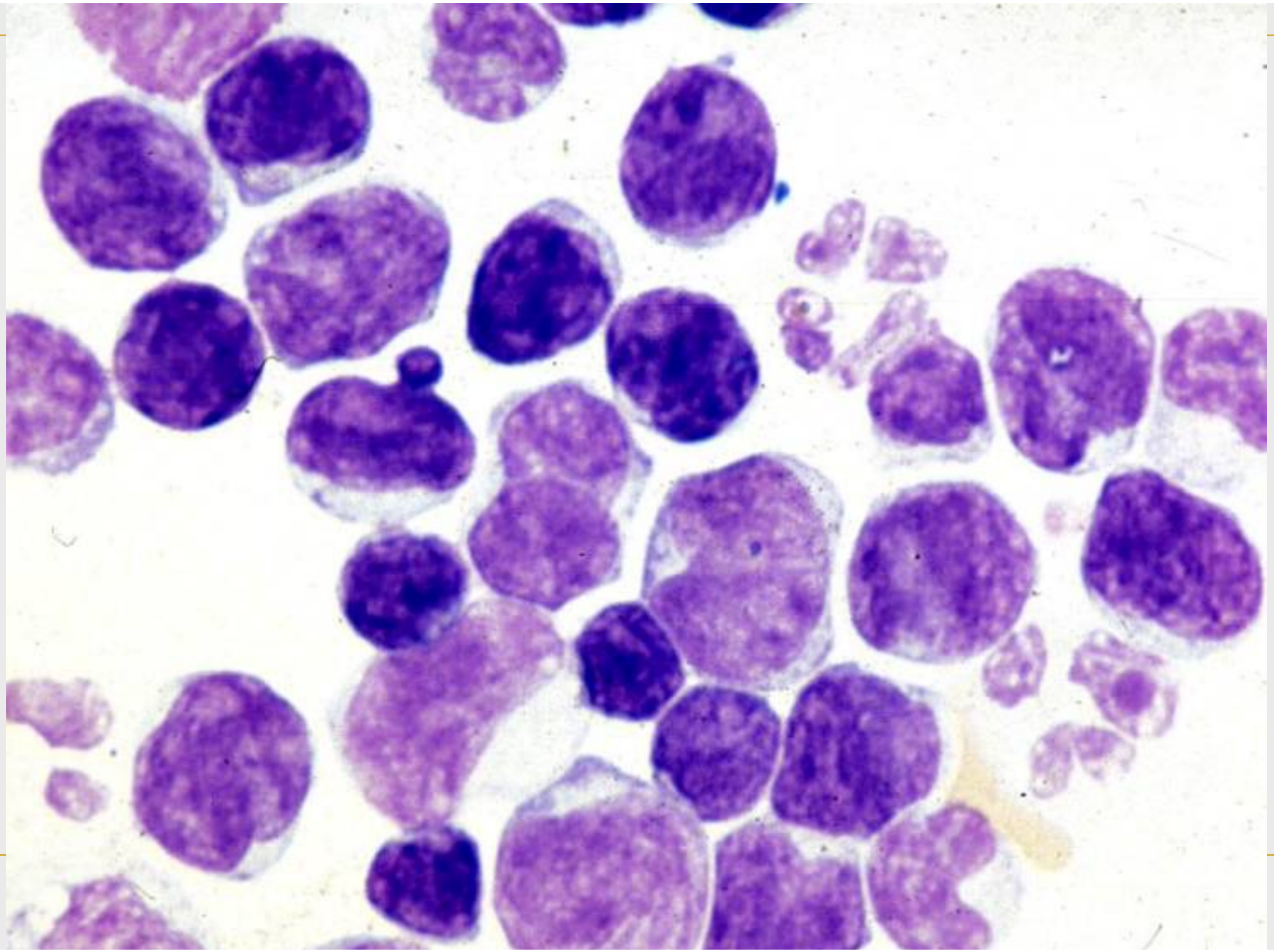


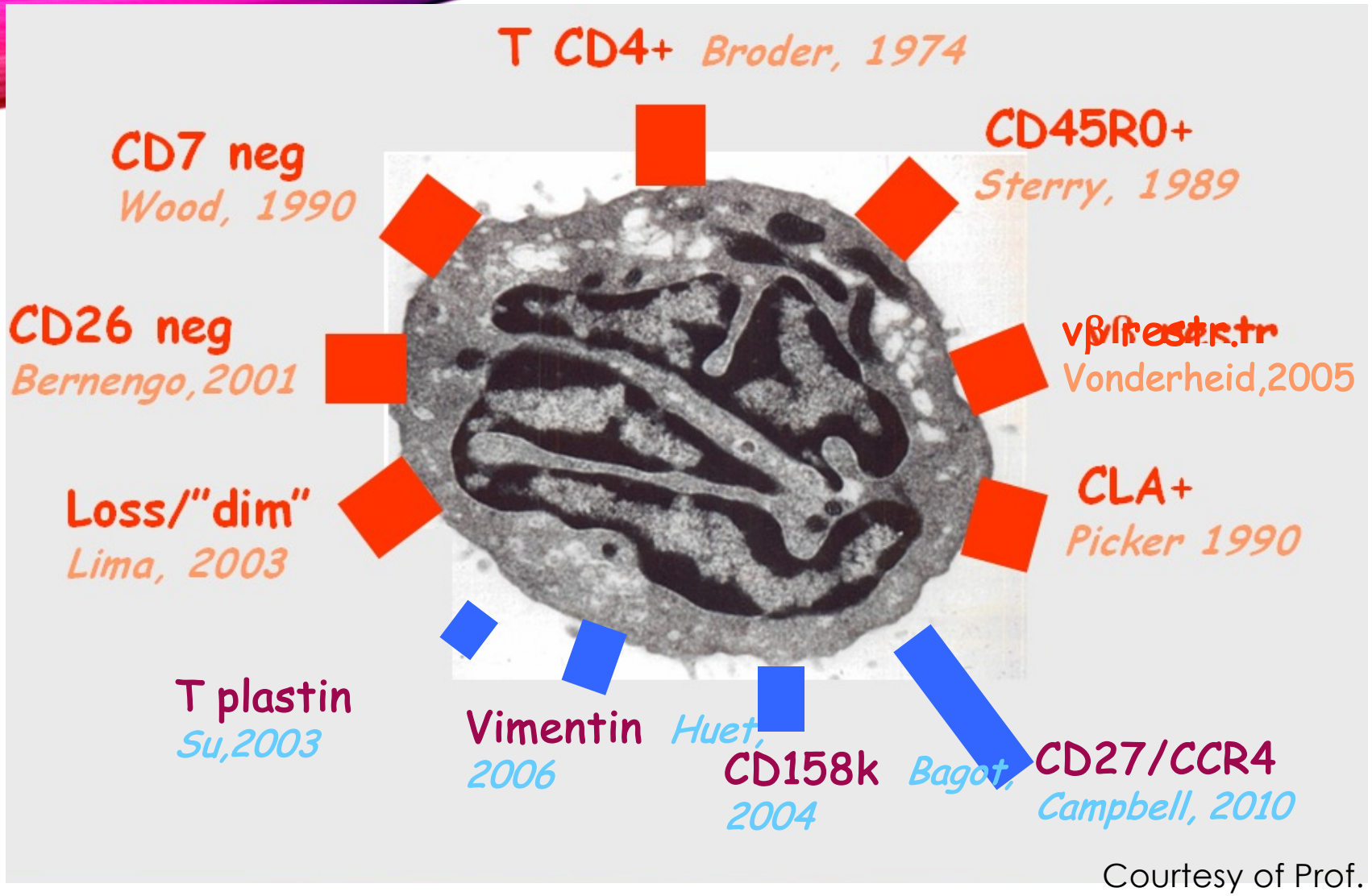




Sézary A, Bouvrain Y : Erytrodermie avec présence de cellules monstrueuses dans le derme et dans le sang circulant . 1938; Bull Soc Fr Derm Symph 45:254.

Baccaredda A : Reticulohistiocytosis cutanea hyperplastica benigna cum melanodermia. 1939 ; Archiv Dermatol Sifil 179:210.

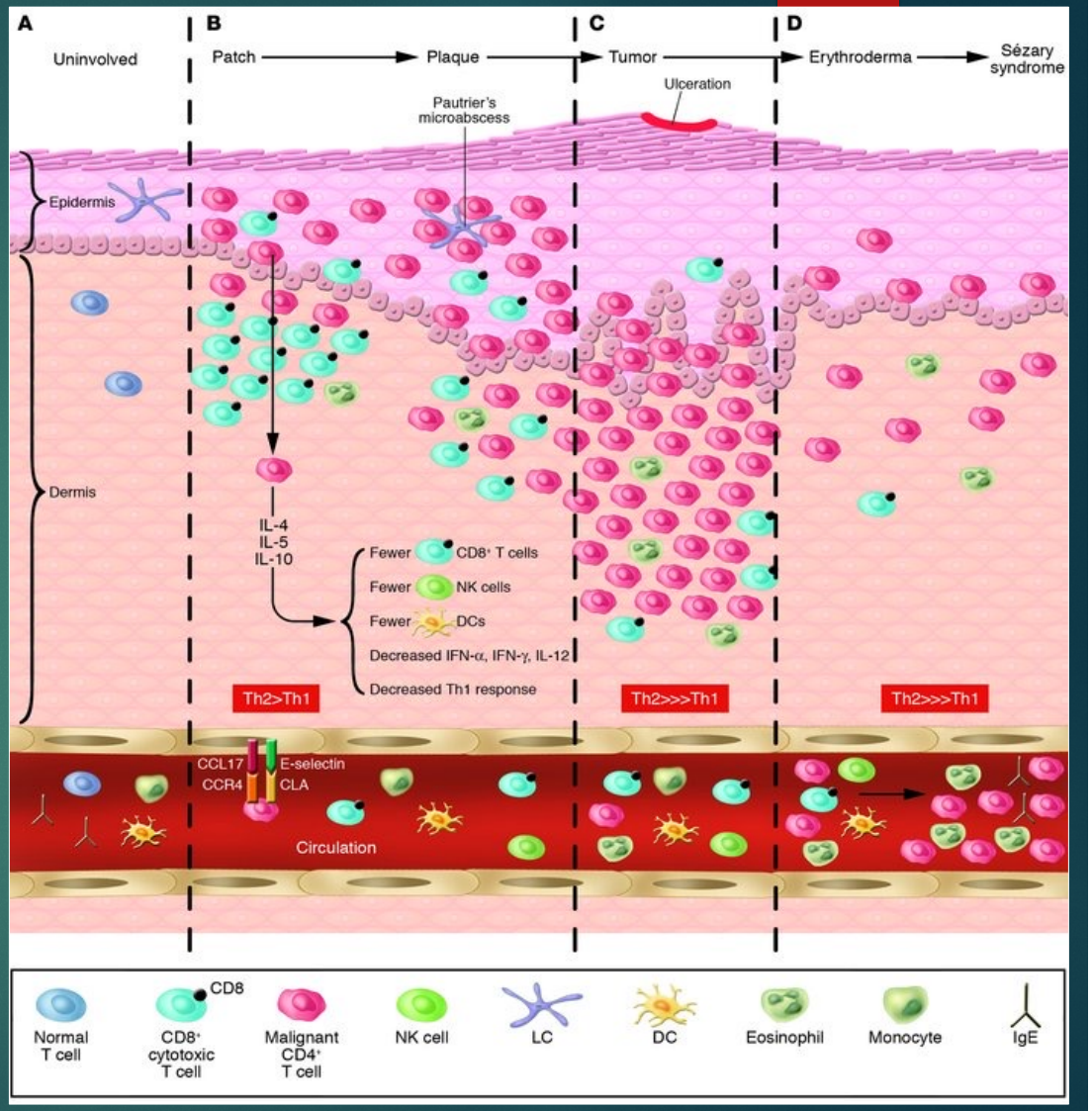




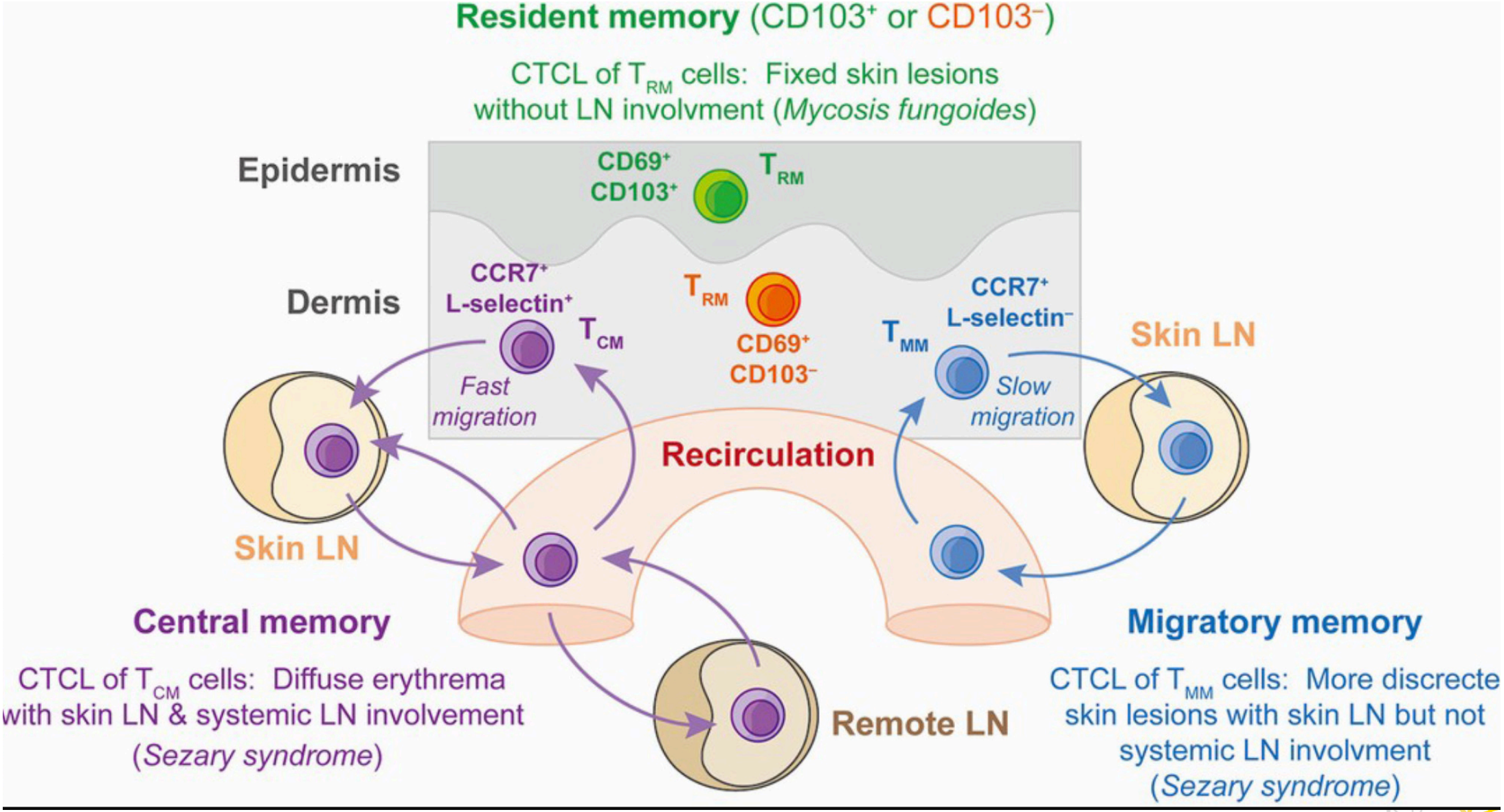
Courtesy of Prof. Quaglino

MF/SS microenvironment

- Early MF
  - Th1 profile
  - IL2, IFNγ , Tbet
  - antitumor immune response
- Advanced MF/SS
  - Th2 profile
  - IL4, IL5, IL10 , GATA3
  - immune failure



Kim EJ.et al. J Clin Invest. 2005;115(4):798-812


Resident memory (CD103+ or CD103−)
CTCL of TRM cells: Fixed skin lesions without LN involvment (Mycosis fungoides)
Epidermis
Dermis
CD69+ CD103+
TRM
CCR7+ L-selectin+
TCM
Fast migration
TRM
CD69+ CD103−
TMM
CCR7+ L-selectin−
Slow migration
Skin LN
Skin LN
Recirculation
Remote LN
Central memory
CTCL of TCM cells: Diffuse erythrema with skin LN & systemic LN involvement (Sezary syndrome)
Migratory memory
CTCL of TMM cells: More discrecte skin lesions with skin LN but not systemic LN involvment (Sezary syndrome)

T Naive	CD45RA+ CCR7+CD62L+ CD27+CD28+	
TCM	CD45RO+ CCR7+CD62L+ CD27+CD28+	Encounter antigen, self-renewing, homing to secondary lymphoid tissues

«cell origin» theory

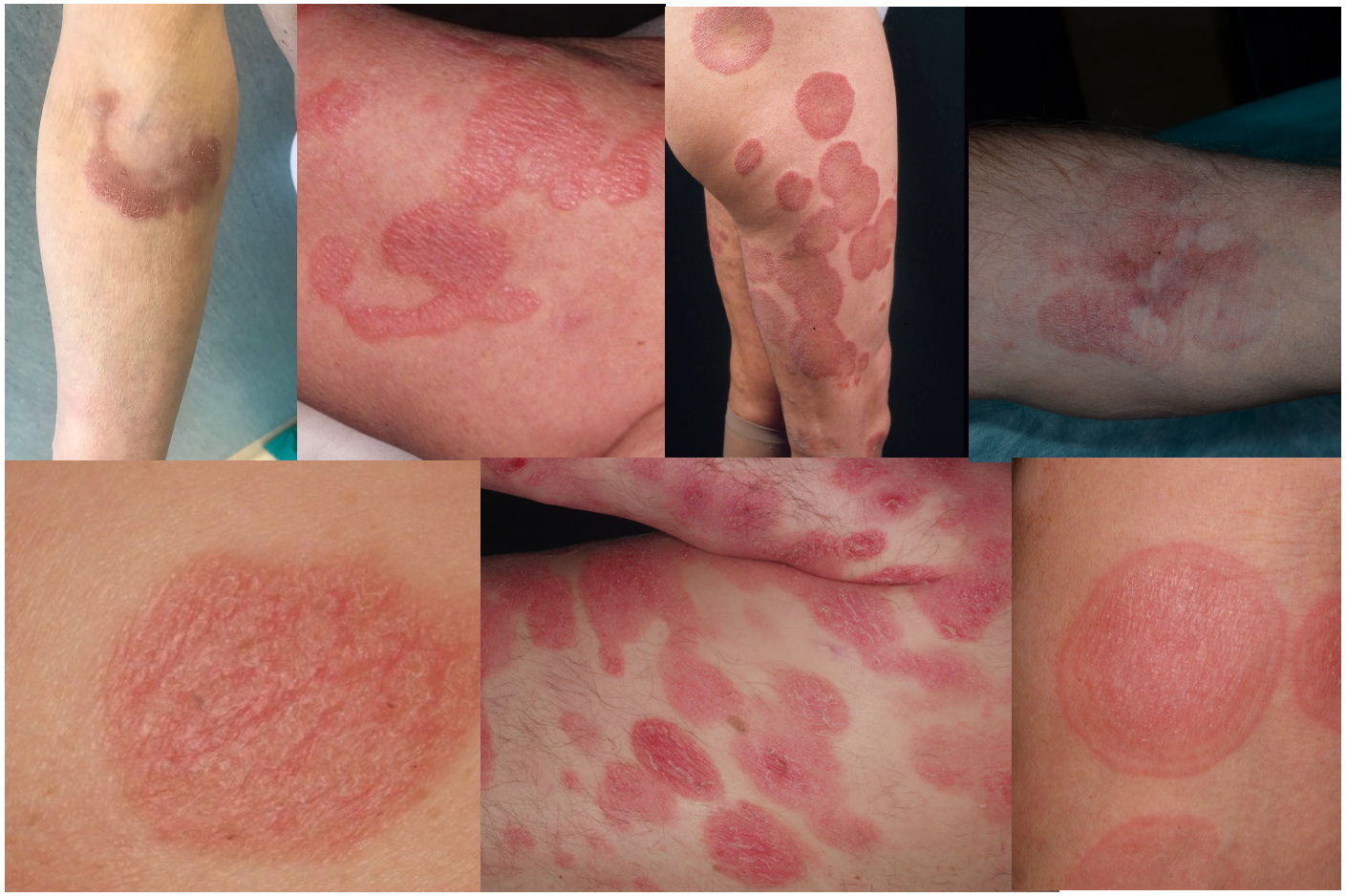
Cytometry Part B (Clinical Cytometry) 96B:234–241 (2019)

Original Article

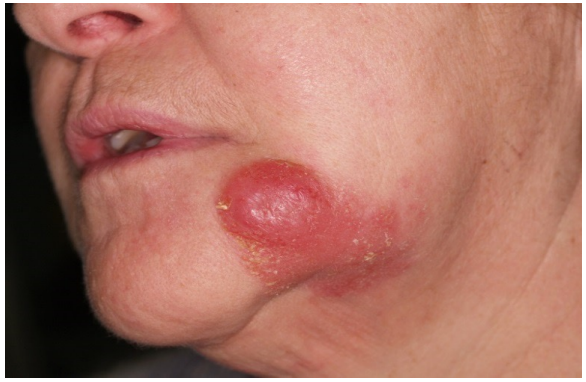
Naïve/Memory T-Cell Phenotypes in Leukemic Cutaneous T-Cell Lymphoma: Putative Cell of Origin Overlaps Disease Classification

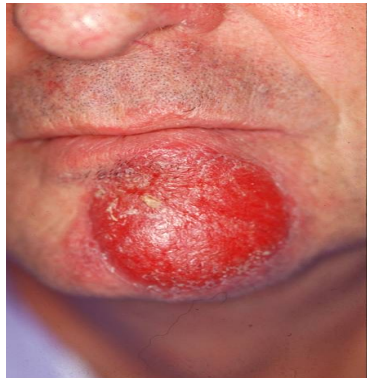
Pedro Horna,[1] Lynn C. Moscinski,[2] Lubomir Sokol,[3] and Haipeng Shao[2]*

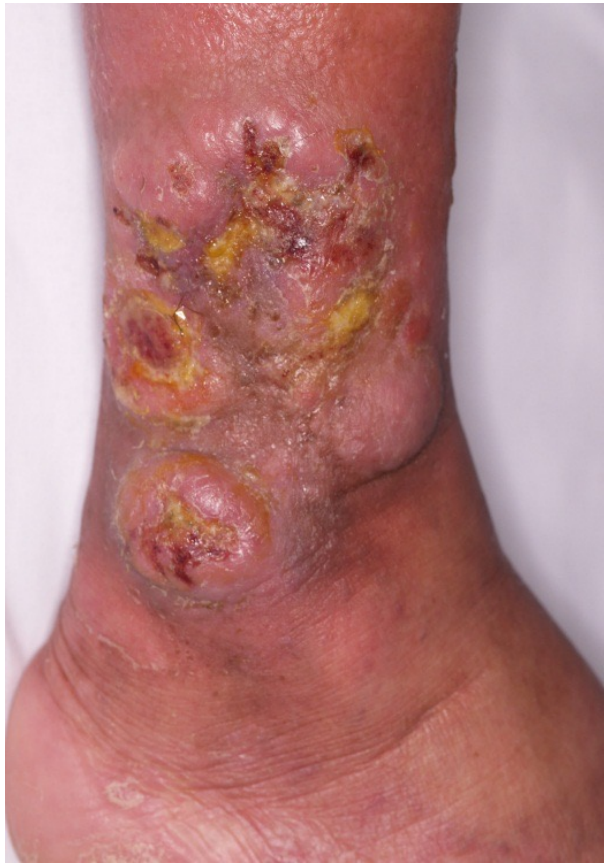
MF - PLAQUE

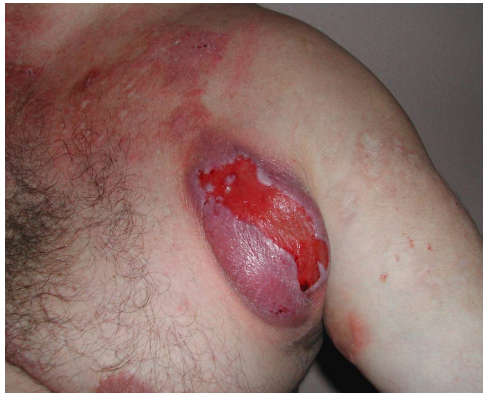


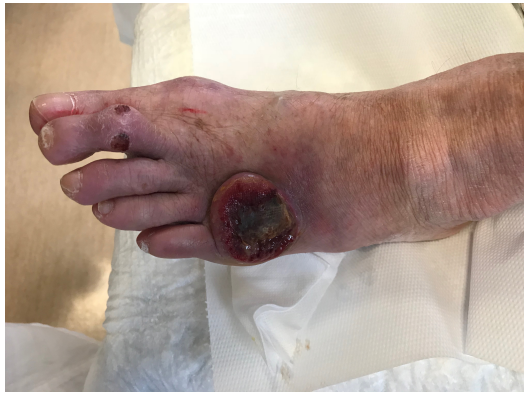
MF - TUMOR



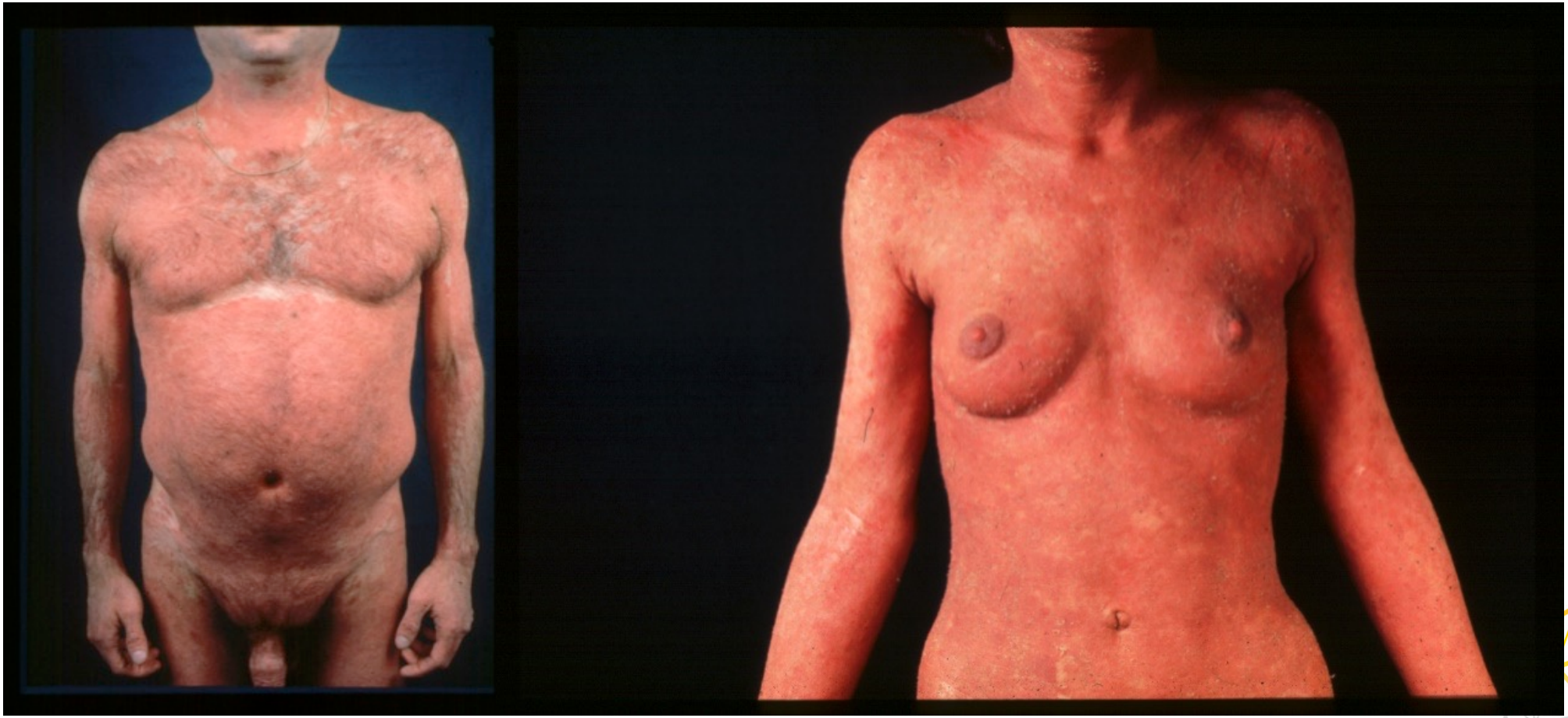


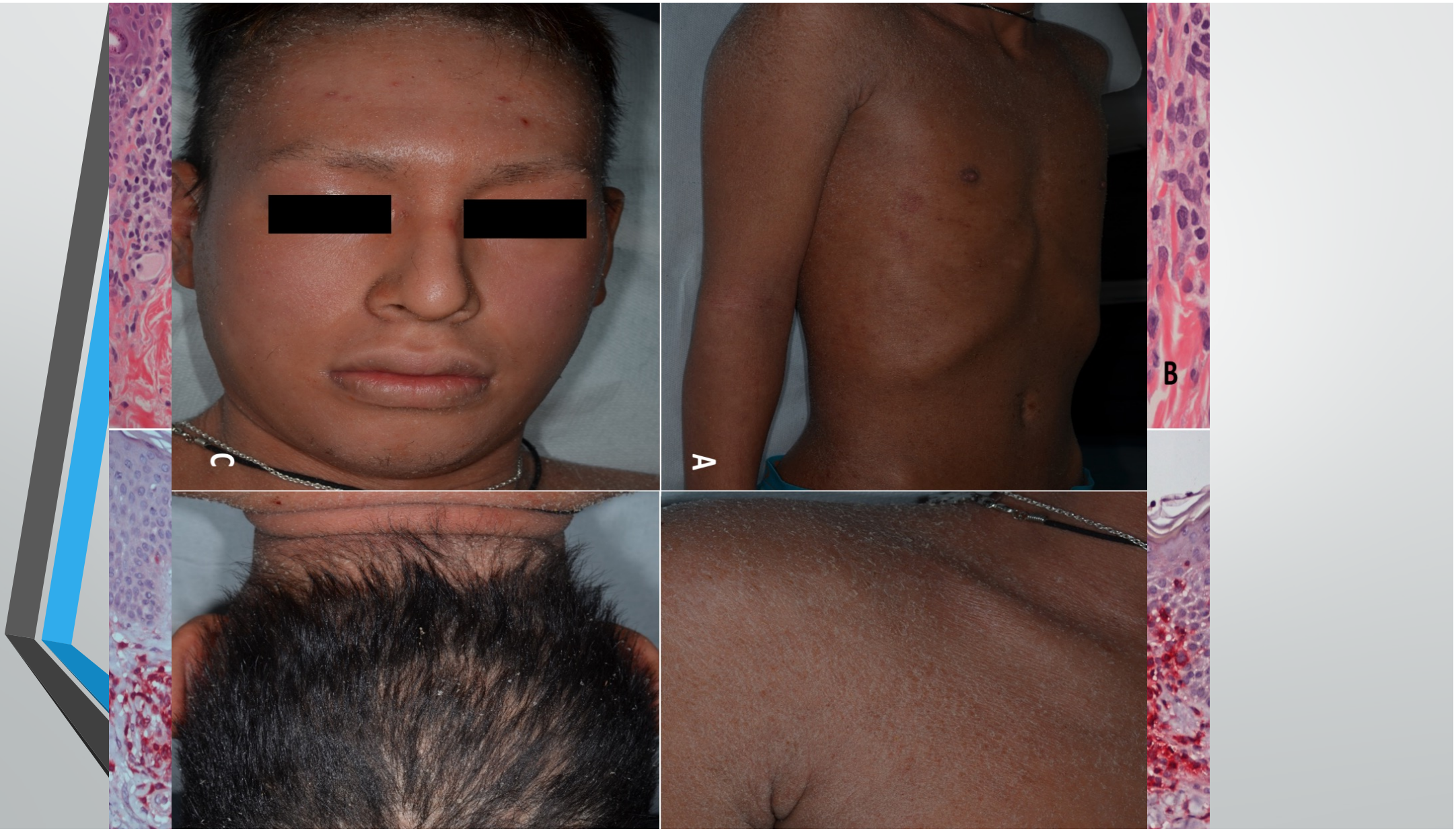




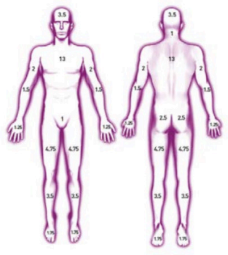


MF - ERYTHRODERMA




A
B
C

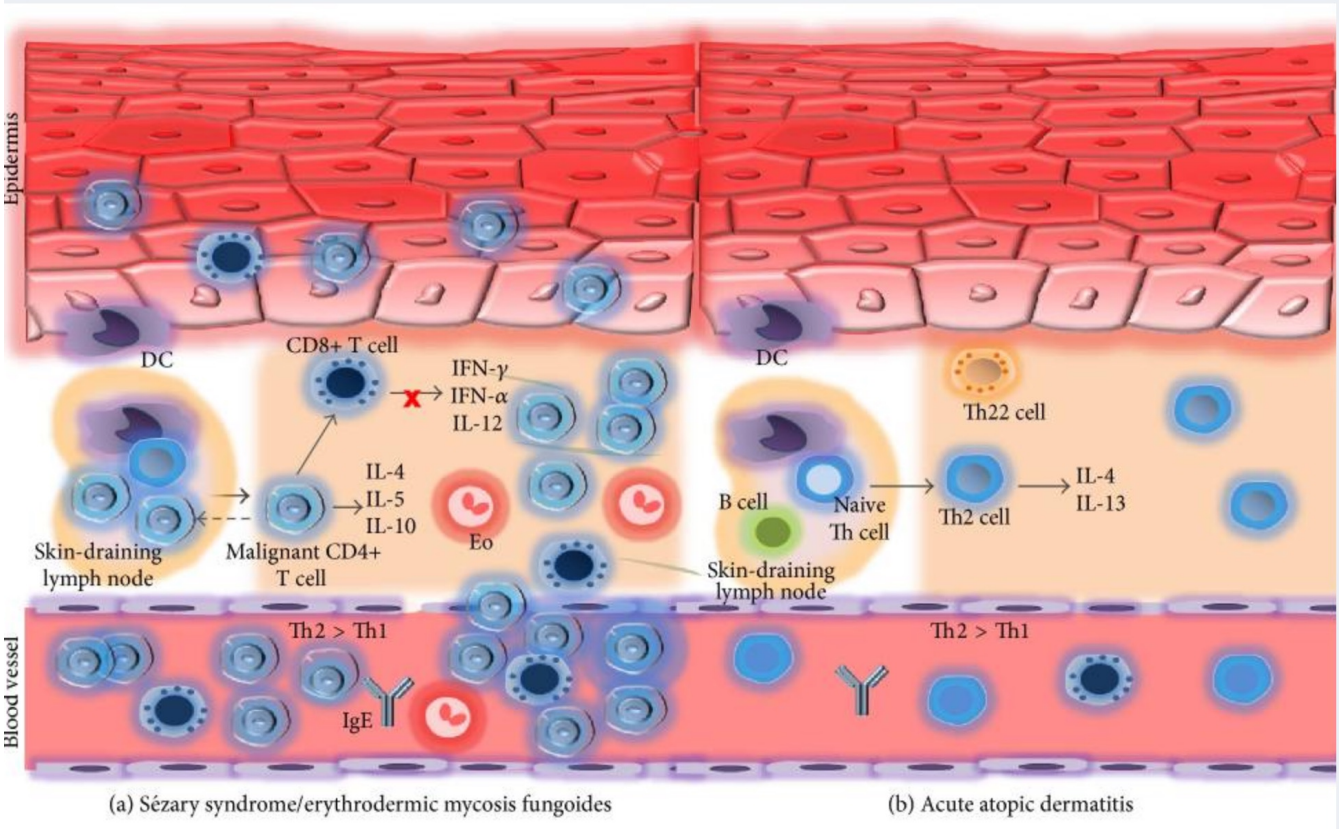
MODIFIED SEVERITY WEIGHTED ASSESSMENT TOOL (MSWAT)



- The body is divided into 12 regions with pre-assigned percentages of total body surface area (BSA).
- The extent of skin disease is assessed for each region and weighted for more severe lesion per the assessment table below.
- The patient's palm (including four fingers and thumb), measured from wrist to fingertips is approximately 1% of total BSA.
- The mSWAT provides a numerical score of skin involvement between 0–400.

		Assessment of involvement in patient's skin		
Body region	**% BSA in Body region**	**Patch[a]**	**Plaque[b]**	**Tumour[c]**
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA weighting factor		**×1**	**×2**	**×4**

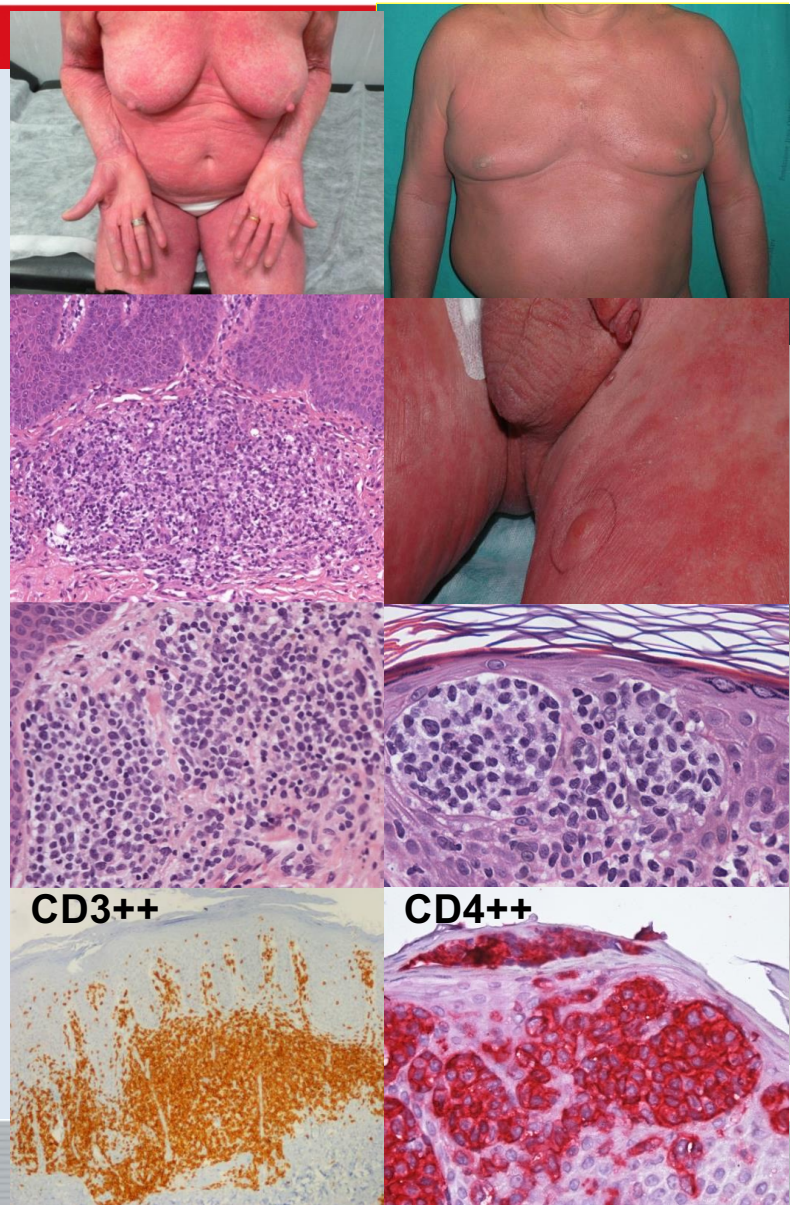
Leukemic CTCL (SS and eMF) and acute AD have both predominance of Th2 immune response

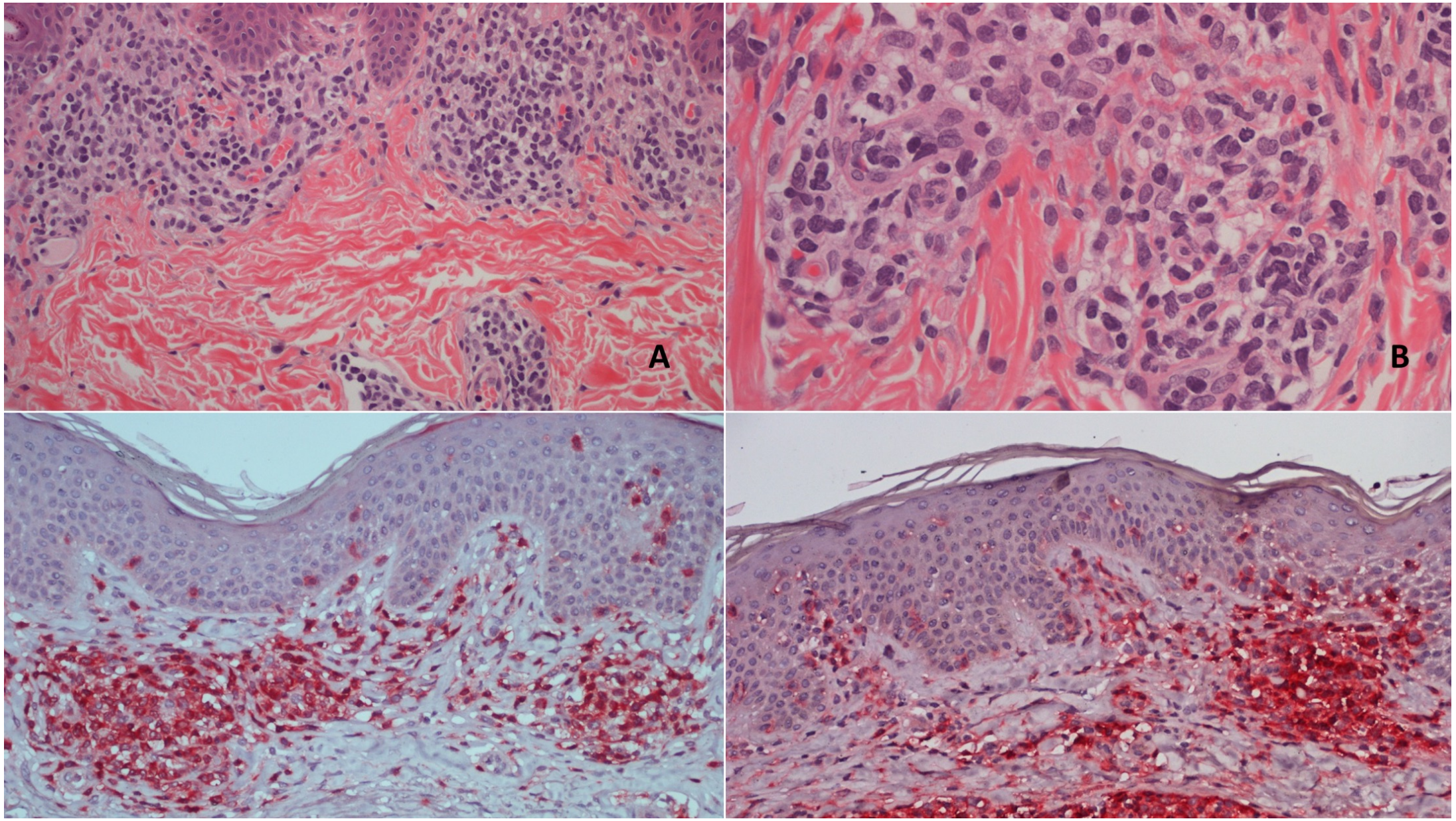


Saulite I, et al. Sézary syndrome and atopic dermatitis: comparison of immunological aspects and targets. Biomed Res Int 2016;epub.

Sézary Syndrome (aggressive)

- Sézary Syndrome is a *leukemic* form of cutaneous T-cell lymphoma (*CTCL*) defined by: *erythroderma*, l*ymphadenopathy* and *peripheral blood involvement; the same neoplastic clone* is detected in skin, lymph nodes and in the blood.
- Sézary syndrome (SS) and MF thanks to different cellular origin and immunoprofile (with specific chromosomal imbalances in SS) are now considered two different diseases, but overlap exists with E-MF.



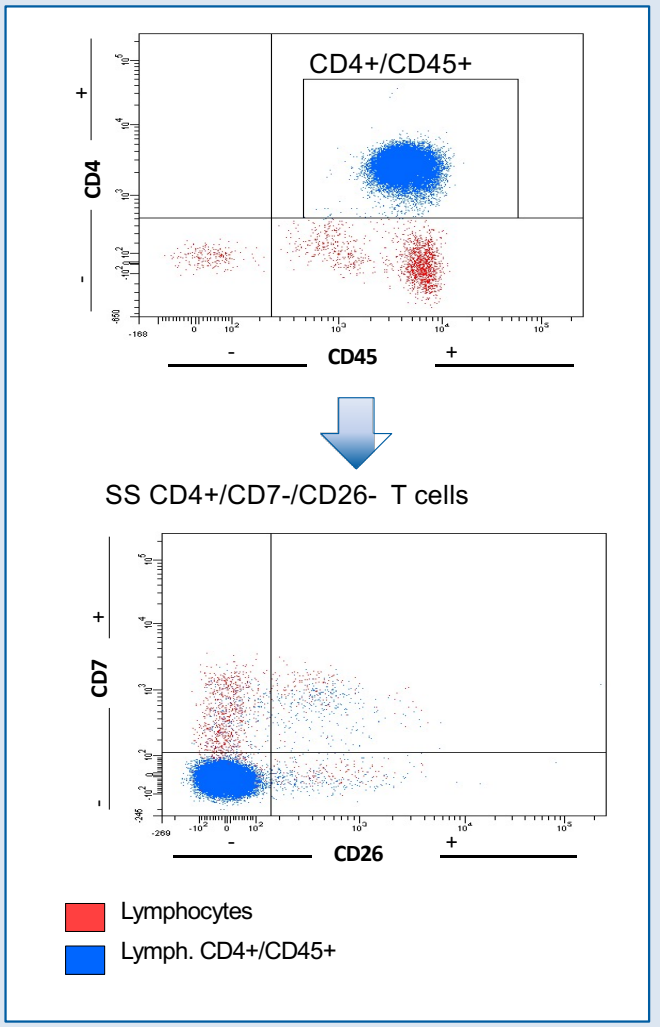

A
B

SÉZARY SYNDROME

- A leukemic form of cutaneous T-cell lymphoma (*CTCL*) defined by:
    1. *Erythroderma*
    2. *lymphadenopathy*
    3. *peripheral blood involvement (B2 stage)*
- B2 stage:
    1. *Monoclonal TCR*
    2. ***≥ 1000/****µl Sézary cells*
    3. *increased CD4+ and CD3+ with CD4/CD8* ***≥ 10***
    4. *increased CD4+ with aberrant phenotype (****≥*** *40% CD4+/CD7- or* ***≥*** *30% CD4+/CD26-*
- Clonal proliferation of central memory T-cells
- OS 5 yrs: 11%

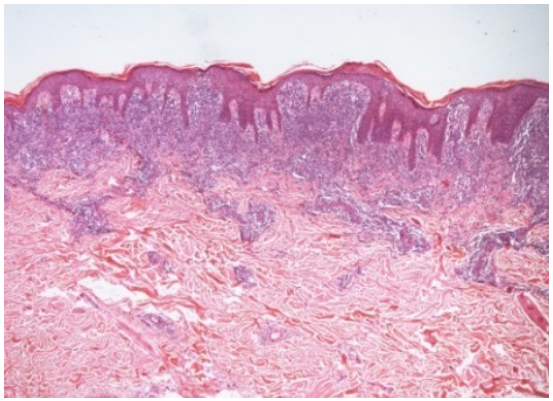
Sézary syndrome/diagnostic workup

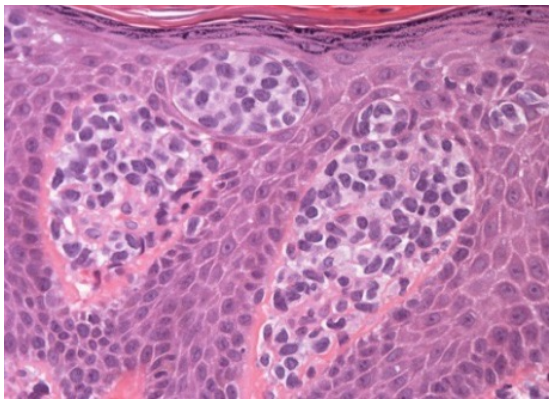
- ☐ Skin biopsy histology, histochemistry and clonality for TCRγ (heteroduplex or GeneScan analysis by using PCR and BIOMED-1/2 primers/protocol).
- ☐ Peripheral blood flow cytometry looking for Sézary cells (manual review), for lymphoid subsets (CD4/CD8 ratio), and for Sézary cells phenotype (CD4+, CD7-/+, CD26-) or for analysis of subfamilies of TCR-β.
- ☐ TCRγ/β clonality evaluation on total lymphocytes or better on separated CD4+ T-lymphocytes.
- ☐ BOM aspirate and biopsy: histology, immunohistochemistry, flow cytometry on aspirate, PCR for clonality, as cited above.
- ☐ Lymph-node biopsy: histology, immunohistochemistry, flow cytometry and PCR for clonality.

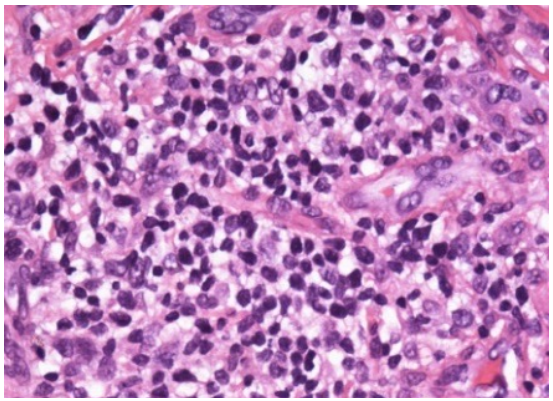


HISTOLOGICAL AND MOLECULAR FINDINGS

- A neoplastic infiltrate of medium to large cerebriform cells can be detected in the superficial dermis (with a dense perivascular distribution) and in the epidermis (forming Pautrier microabscesses).
- No specific histologic features are possible
- Immunophenotype: CD2+, CD3+, CD4+, CD5+, CD7-/+, CD26-, CD27+, CD45RO+, TCRβ+, CCR4+, CD30-, CCR7+ L-selectin+ (*central memory T cells*), PD1+, CD30+/- (>33% of cells) ; rare cases may be CD4-/CD8- or CD8+.
- The same T-cell clone in the skin, blood and lymph-nodes
- Detection of the same T-cell clone (by TCR-β analysis) in the skin, blood and lymph-nodes and of the cytogenetic SS profile (arrays-CGH): gains of 8q23-24.3, 17q23-24 and losses of 9p21, 10p12-11.2,, 10q22-24, 10q25-26, 17p13-q11. (Lahranne et al J. Invest. Dermatol. (2010) 130, 1707-18).



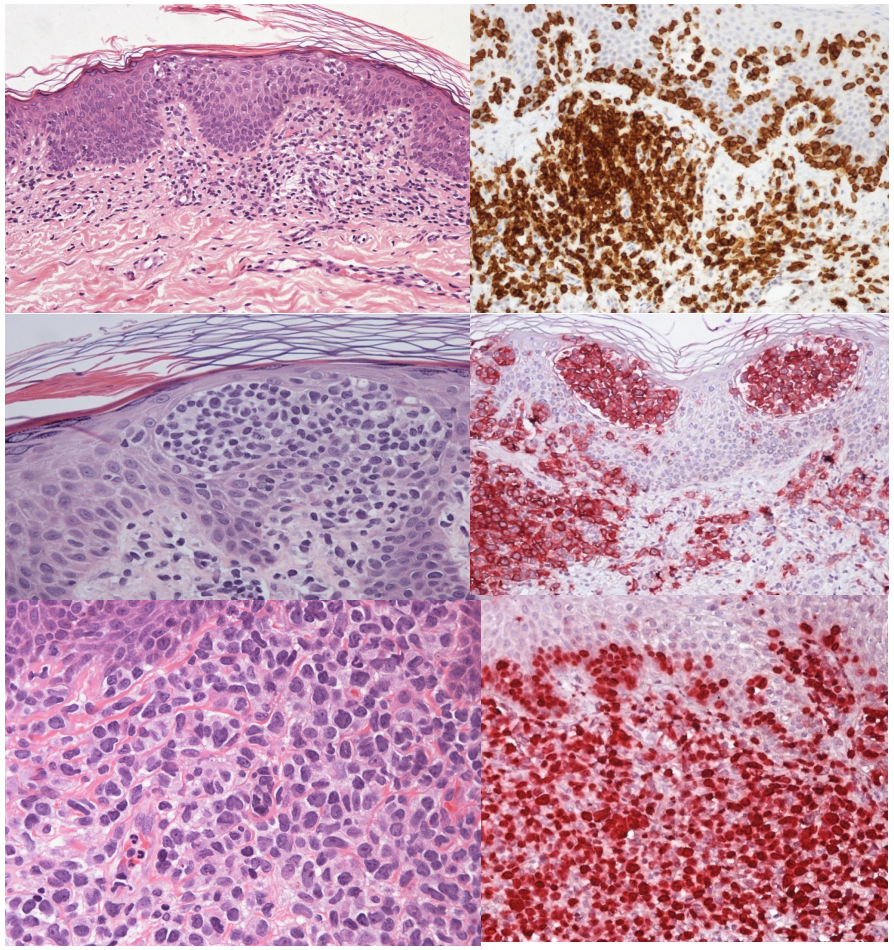




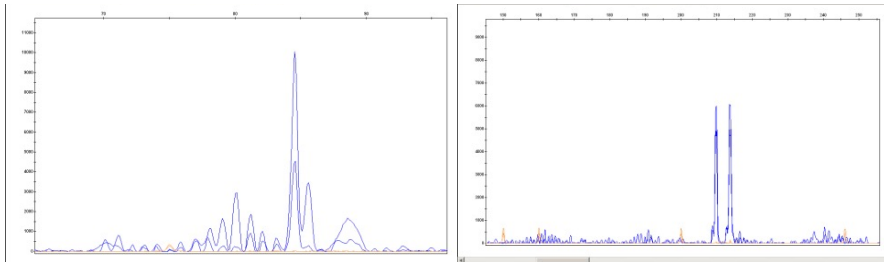
MYCOSIS FUNGOIDES

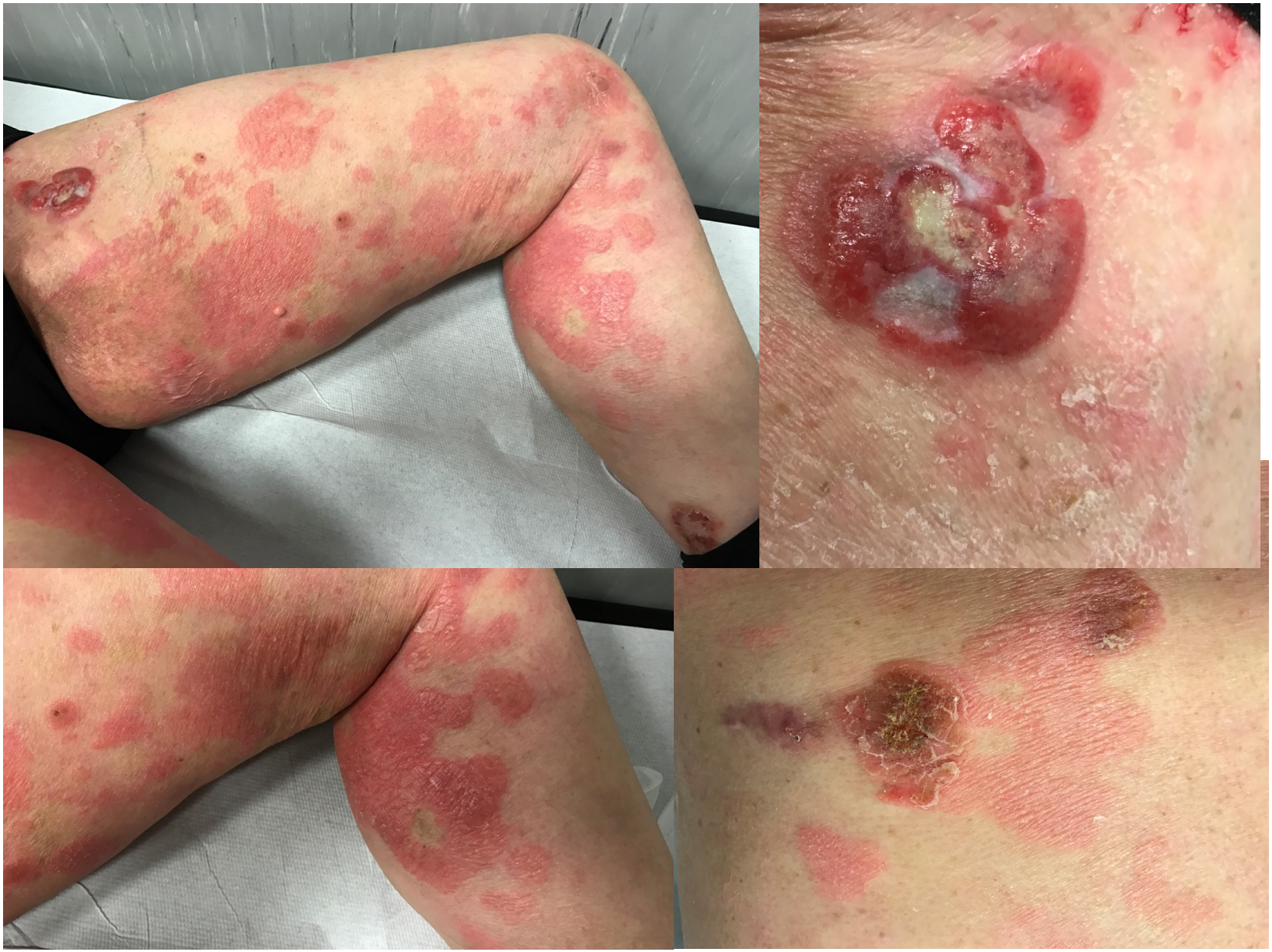
Neoplastic T-cells are

- **positive for βF1, CD3, CD4, CD45RO, CCR4**
- Negative for CD7, CD8, CCR7/L-selectin, CD27).
- Less frequently MF cells may express CD8+ and cytotoxic markers (Tia-1+, Granzyme-B+, Perforin)

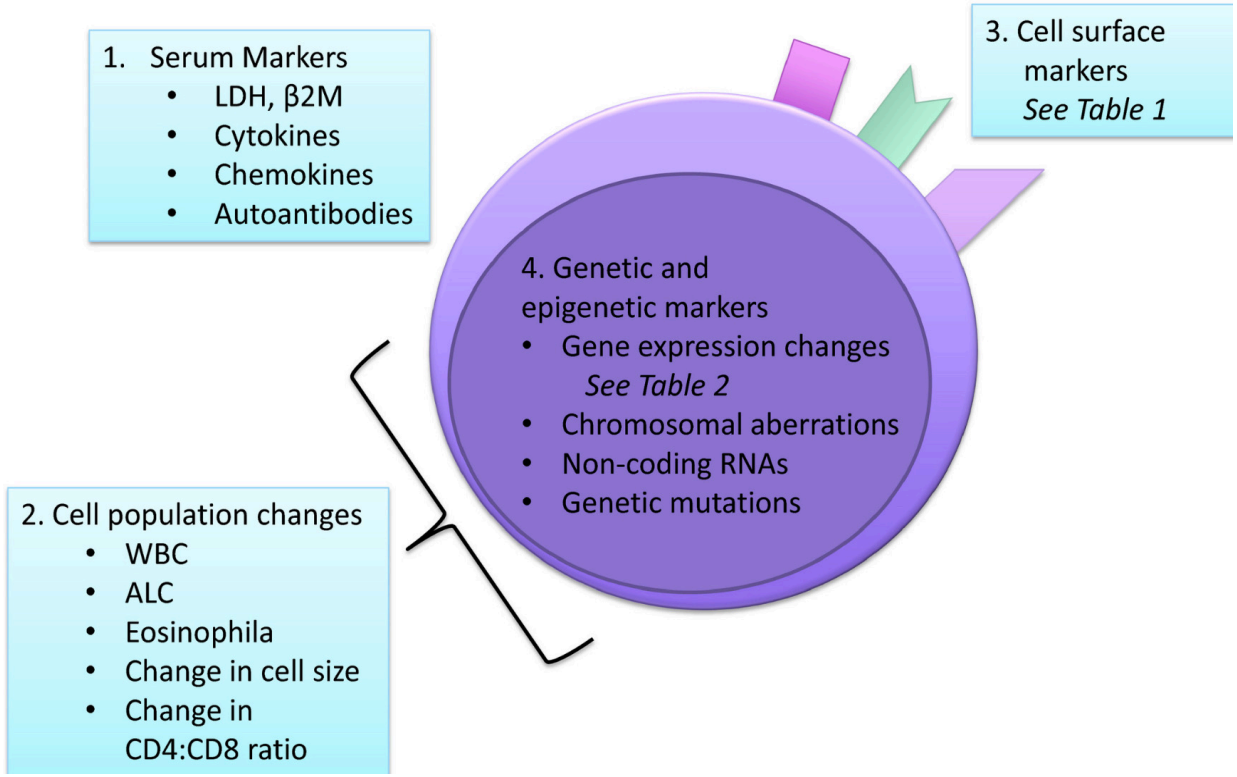


Molecular analysis by using PCR shows monoclonal rearrangement of the TCR





BIOMARKERS IN MF AND SS



Dulmage B, et al. Exp Dermatol 2017;26(8):668-78.

Primary cutaneous small-medium sized pleomorphic CD4+ T-cell LPD

- Rare, provisional entity

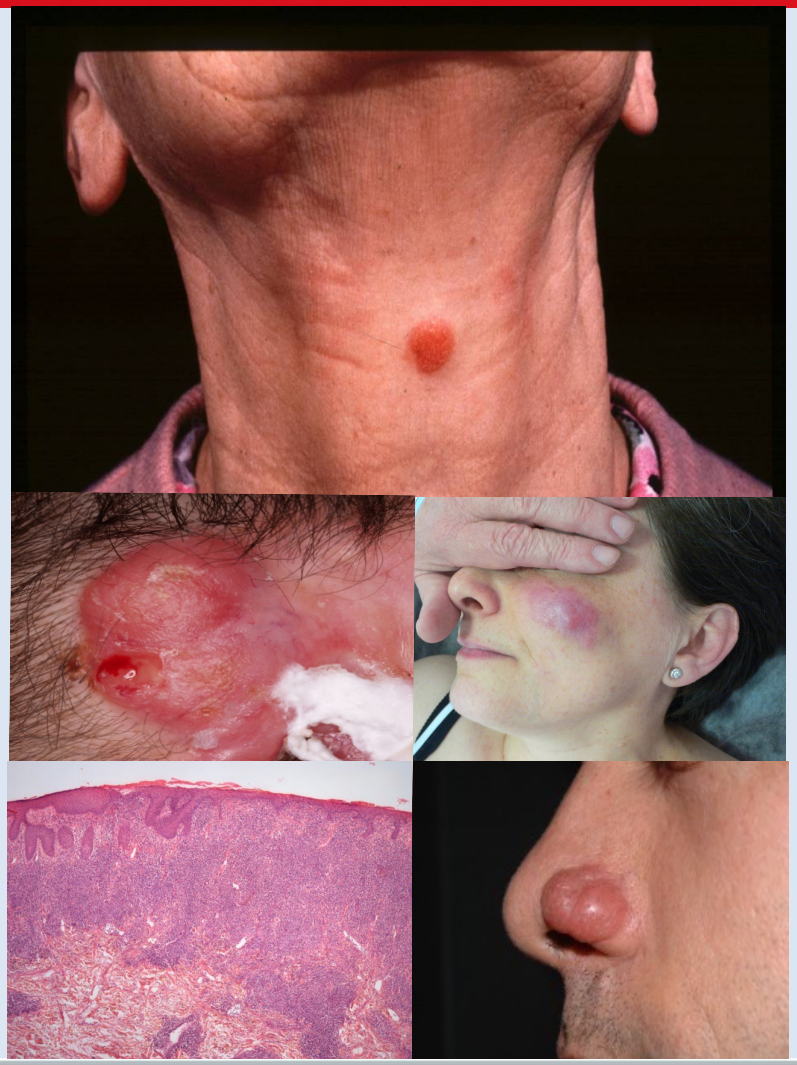
- Solitary nodule or plaque; more frequent on head and neck

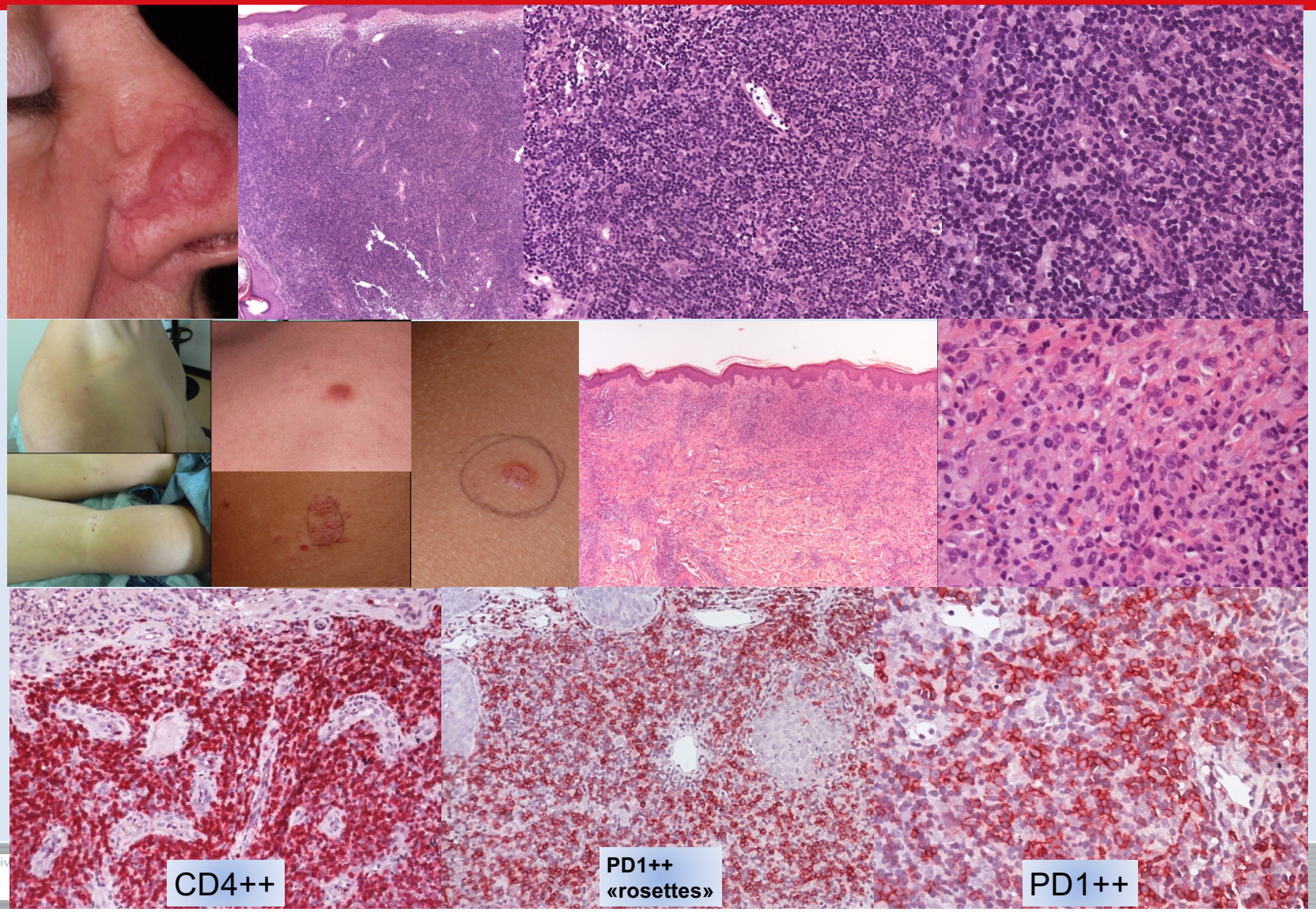
- No systemic symptoms

- Favourable outcome, OOS 5y 100%

- Dense, nodular/diffuse angiotropic dermal infiltrate, focally epidermotropic, small/medium sized pleomorphic cells

- Immunoprofile: CD3+, CD4+, CD8-, CD30-, EBV-, PD1+ (rosettes of + cells)




CD4++
PD1++
«rosettes»
PD1++

CD4+ SMALL/MEDIUM-SIZED PLEOMORPHIC T-CELL LPD: RE-EVALUATION OF 33 CASES

L. Corti[1], V. Merlo[1], L. Venegoni[2], D. Fanoni[1], S. Alberti-Violetti[1,2], E. Berti[1,2]

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano; [2]Università degli Studi di Milano

Introduction

Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma (PC-CD4-SMPTL) is a provisional entity in WHO/EORTC classification characterized by a predominant proliferation of small to medium-sized CD4 positive pleomorphic T-cells and with a broad differential diagnosis.

A majority of cases present with a solitary plaque or nodule on the face, neck or upper trunk in absence of preceding patches and plaques of mycosis fungoides.

A minority of patients may present with large tumors, or multiple skin lesions.

SMPTL show dense, nodular or diffuse perivascular and periadnexal lymphocytic dermal infiltrates with characteristic hyperchromatic small/medium sized pleomorphic T-cells forming clusters, admixed to reactive B-cells, plasmacells, histiocytes and a variable amount of eosinophils. Epidermotropism may be present focally.

These lymphomas usually have a favorable prognosis. Surgery or local [illegible] treatment.

Aim

The purpose of this retrospective study was to re-evaluate clinical, histological and molecular features of PC-CD4-SMPTL patients collected in our Hospital since 1994, in order to better understand diagnostic approach and prognostic factors.

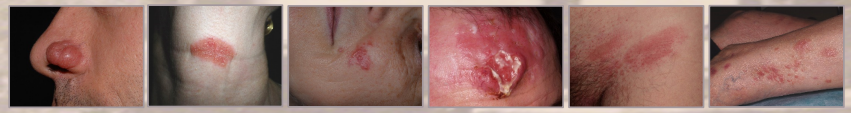
Patients

Thirty-three patients were included in this study: 14 M (42,4%) and 19 F (57,6%). Median age at onset of disease was 48 years (range 16-73).

Median follow-up time was 15 months (range 0-180): 32 patients were alive without evidence of extracutaneous disease at last follow-up, one, with disseminated lesions, died of pneumonia 74 months after the onset of symptoms. The main treatments used were local radiotherapy, surgical excision, phototherapy (UVB-NB) and topical steroids with benefits. About 20% of patients had a waxing and waning course.

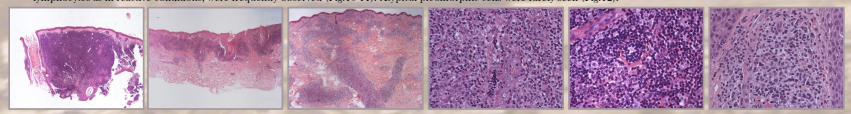
Clinical Presentation

16 of patients (Fig.1) presented with a single nodule on the nose, face or neck (48,5%); 9 showed a solitary plaque (Fig.2) or nodule in other body areas; 1 localized multiple papules on the face (Fig.3); 1 multiple localized nodules on the forehead (Fig.4); 6 multiple lesions similar to mycosis fungoides early stages (Fig.5 and 6).



Histology

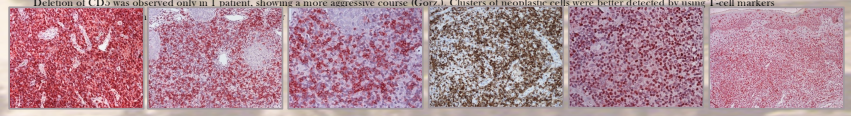
Most of cases with typical presentation shared the same histologic features, showing a nodular perivascular and periadnexal lymphocytic dermal infiltrate (Fig.7) with characteristic hyperchromatic small/medium sized pleomorphic T-cells forming clusters, admixed to reactive B-cells, plasmacells and histiocytes. In the other cases the multi-nodular perivascular-periadnexal lymphocytic infiltrates was located in superficial dermis (Fig.8), deep dermis or both (Fig.9); eosinophils and intravascular lymphocytes as in reactive conditions, were frequently observed (Fig.10-11). Atypical pleomorphic cells were rarely seen (Fig.12).



Immunohistochemistry

In all cases proliferating T-cells had a CD3+, CD4++(Fig.13), CD8-, CD30-, PD1+ (30-50% of cells) (Fig.14-15), Bcl2+ (Fig.16), Bcl6+ (50%) (Fig.17), Tbet+(Fig.18),MIB1/Ki-67+/- (5-10%) immunophenotype.

Deletion of CD5 was observed only in 1 patient, showing a more aggressive course (Gorz). Clusters of neoplastic cells were better detected by using T-cell markers



CD4 PD1 PD1 Bcl2 Tbet Bcl6

Molecular Analysis

TCRG genes were **clonally rearranged** in up to 96% of cases.

No consistent cytogenetic abnormalities were identified in 11 cases with different clinical

presentations analyzed by array-CGH.

Conclusions

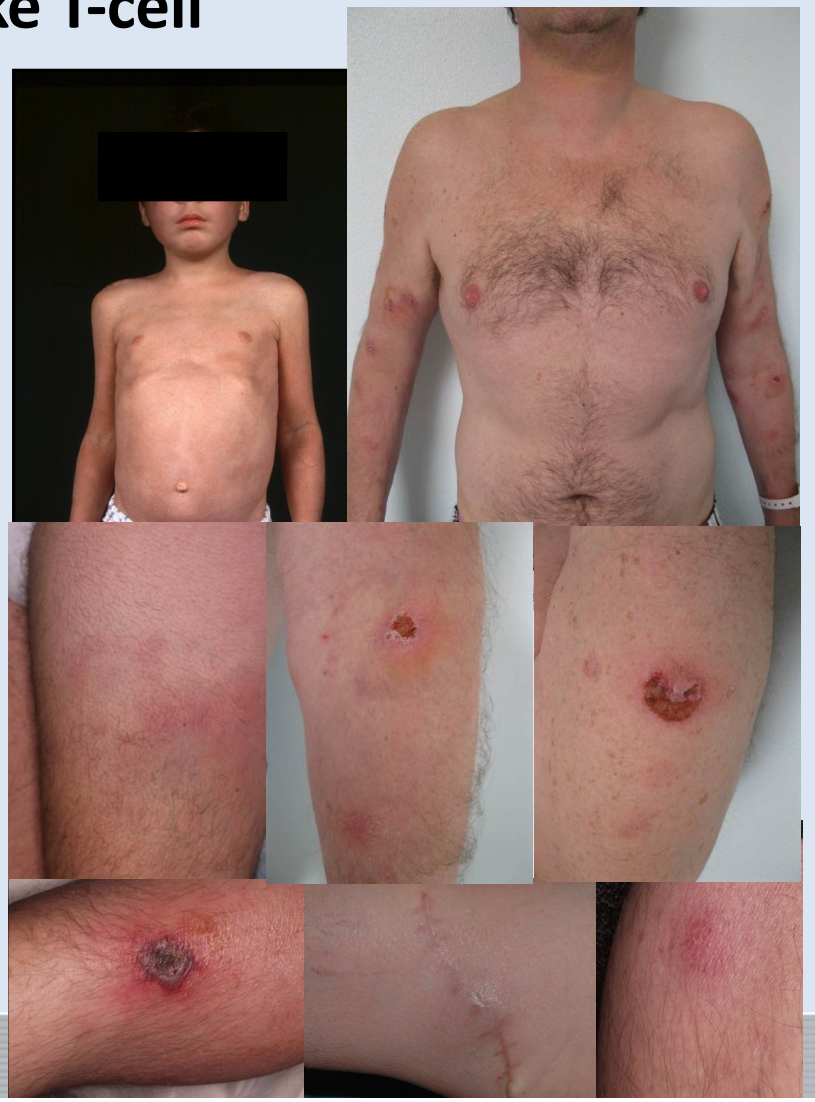
This entity is characterized by a clinical variability and a favorable prognosis in most cases.

Clinical, histopathological, immunohistochemical and molecular study must be done to confirm the diagnosis. Differential diagnosis with pseudolymphomas and other cutaneous

lymphomas with an indolent course, such as mycosis fungoides (particularly in case with multiple lesions) and cutaneous B-cells lymphomas (in the presence of many B-cells)

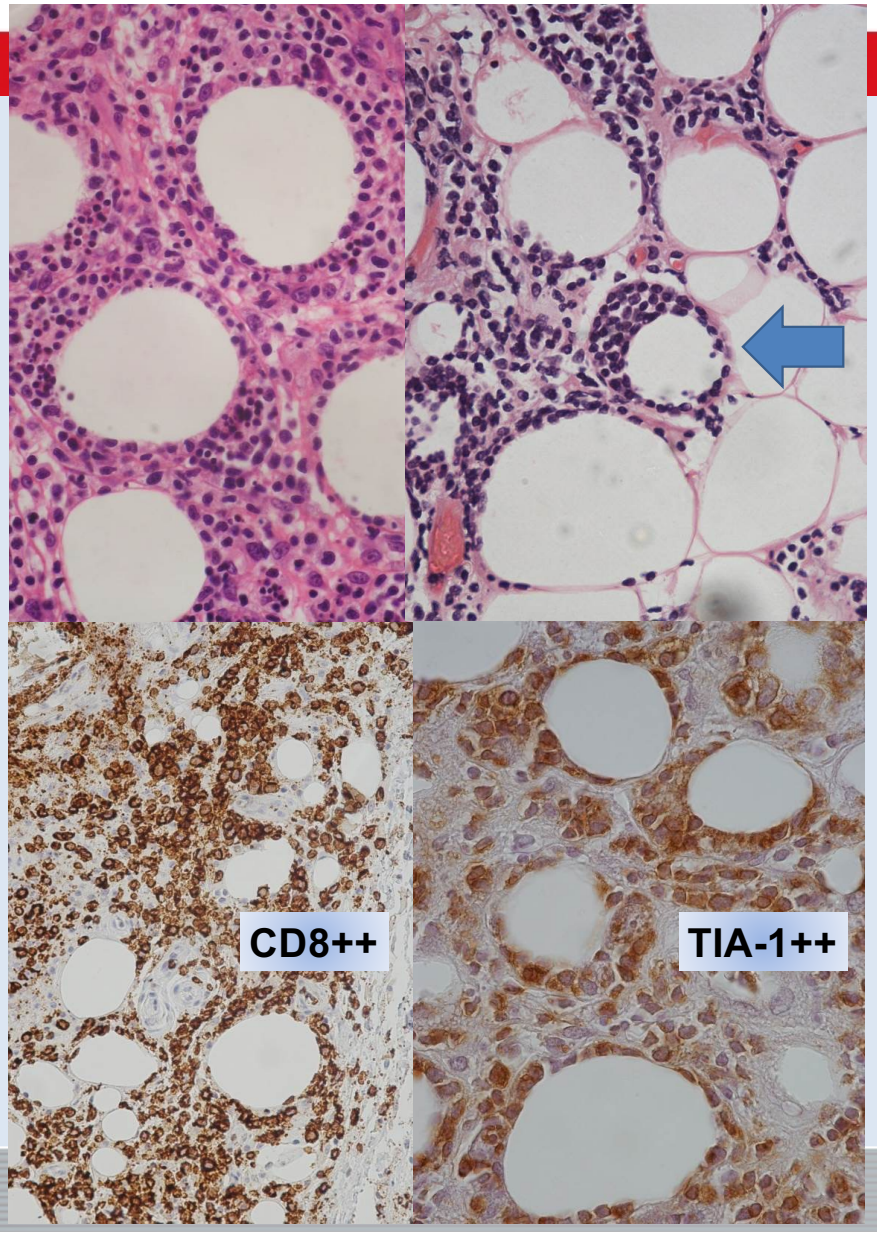
Subcutaneous panniculitis-like T-cell Lymphoma (Indolent)

- Rare: 1% 4th decade of life male/female ratio 0,5.
- 19% of patients being 20 years or younger
- Male/female ratio 0,5
- Subcutaneous nodules, plaques involving the legs and the arms, more rarely diffuse.
- Initially asymptomatic, then B-symptoms frequent.
- 17% develop a haemophagocytic syndrome (more aggressive).
- 5 years overall survival rate is about 82%



Histology

- Low magnification shows a specific “lipotropic “ lymphoid infiltrate in the adipous tissue, usually sparing septa, whole dermis and epidermis. Adipous tissue may be necrotic or hypertrophic.
- Neoplastic cells (small/medium size pleomorphic T-cells) and then macrophages distribute between individual adipose lobules (arrow), proliferating and forming “rim” and “capping” images, around lypocytes, conferring a lace-like appearance.
- **Immunoprofile** (cytotoxic) **βF1+** (TCR-αβ),**CD8+**,CD2+,CD3+,CD5+, **CD45RO+**,**TIA-1+**,Granzyme B+, **EBV-**
- **TCR** rearranged (PCR, GenScan)



Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (AECTCL)

- Rare, a provisional entity.
- Nodules and plaques (Fig.4, 6), haemorragic-ulcerated (Fig.1-3, 5) or hyperkeratotic verrucoid lesions (Fig.2, 7).
- Rapid progression, few months-1 year, sparing superficial lymph nodes.
- Systemic involvement of CNS, testis, oral cavity, heart, spleen,liver, lung and frequent coagulopaty (Fig.8).
- Medium survival 32 months
- Histology: strongly epidermotropic and angiocentric-angiodestructive medium/large pleomorphic, immunoblastic CD8+

  T-cell infiltrate.
- Partial response to multiagent chemotheray or BMT

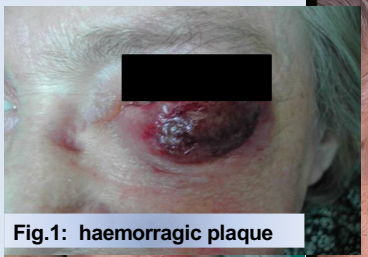


Fig.1: haemorragic plaque

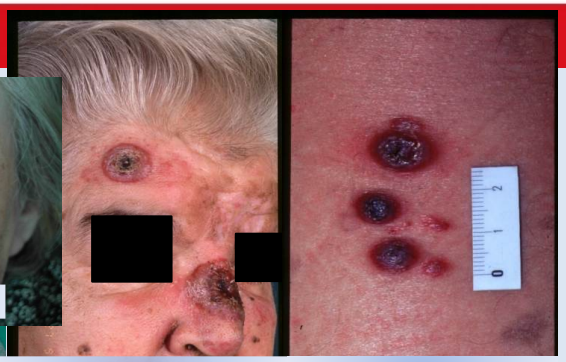


Fig.2: ulcerated verrucoid nodules

Fig.3: typical papulo-nodular necrotic lesions

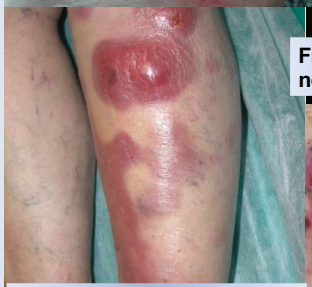


Fig.4: nodules-plaques, D.D. with large-B-cell lymphoma of the leg

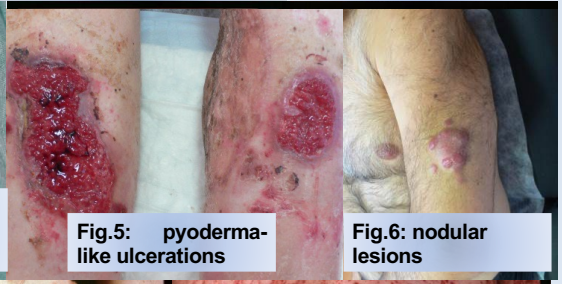


Fig.5: pyoderma-like ulcerations

Fig.6: nodular lesions

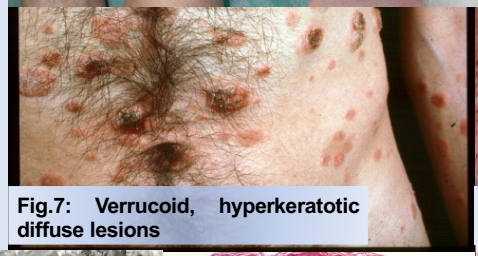


Fig.7: Verrucoid, hyperkeratotic diffuse lesions

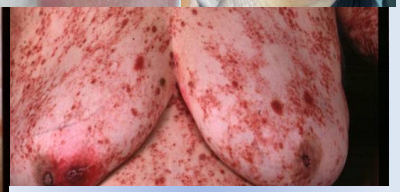
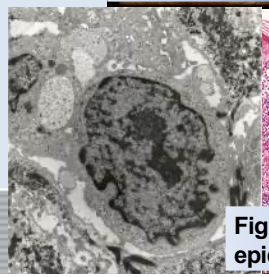


Fig.8: purpuric diffuse eruption (coagulopathy)



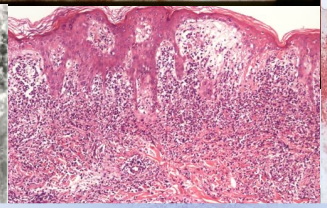


Fig.9: histology: note the highly epidermotropic-angiocentric infiltrate.

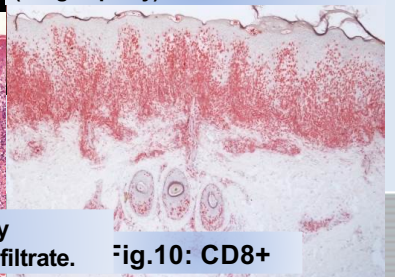


Fig.10: CD8+

AECTCL

Patients suffering from primary cutaneous AECTCL CD8+ T-cell lymphoma :

- Present with localized or disseminated, rapidly growing erosive or ulcerative cutaneous nodules, plaques and verrucoid lesions (see Fig.1-8).

- Histology: tumor cells shows heavy epidermotropism (PR-like), with blister formation or keratinocyte necrosis and an angiocentric-angiodistructive pattern, subcutaneous tissue is frequently involved.

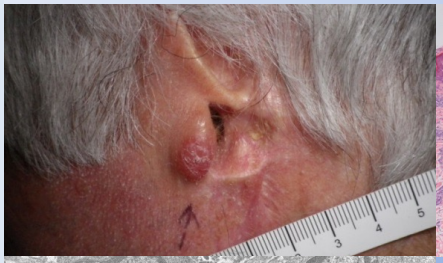
- Immunoprofile is: CD8+, β-F1+ (TCR-αβ), CD3+, CD7+/-, CD43+, CD45RA+, TIA-1+, Granz-B+, Perforin+, EBV-; rare cases are CD45RO+ or CD45RO-/CD45RA-, CD56+, EBV+.

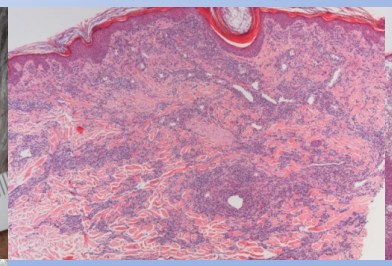
- No treatments guidelines: partial response to multiagent chemotherapy or new polychemotherapy association for CTCL or PTCL/NOS; new agents in clinical experimental studies, allogeneic transplant or non-myeloablative allogeneic transplant, when possible.

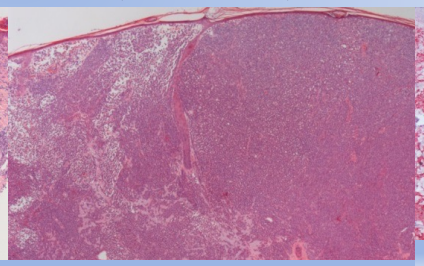
This PTL/NOS provisional entity has to be distinguished from CD8+ MF or CD8+ LYP (type-D). Clinically D.D. with other aggressive NK/T-T-lymphomas

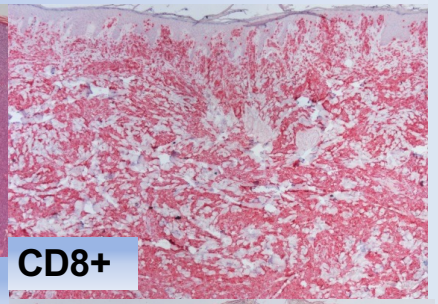
Primary cutaneous acral CD8+ T-cell lymphoma :

Phenotype: CD3+, CD5+, CD8+,CD45RO+, TIA-1+, GR-B-





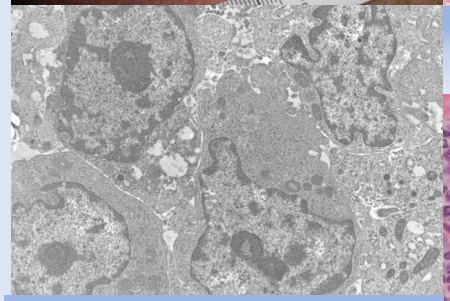




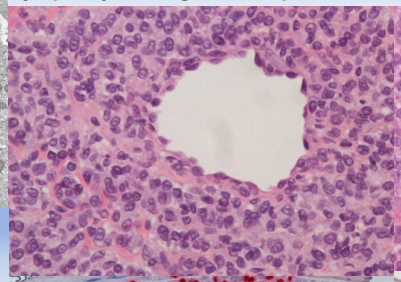
CD8+

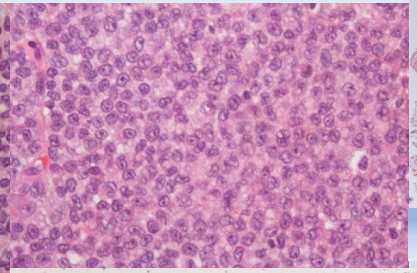
Early lesion: monotonous proliferation of small-medium size lymphocytes: angiocentric pattern

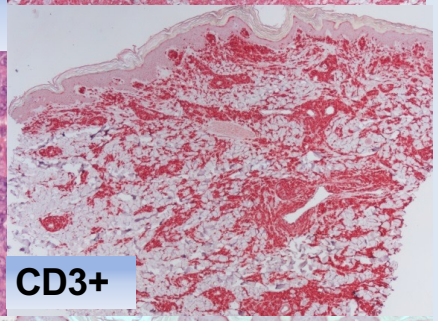
Nodule: proliferation of blasts-like cells with central nucleoli and abundant clear cytoplasm



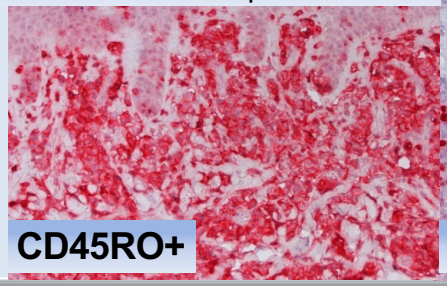
PTL of the Ear: Electron Microscopy showing lymphoid cells with roundish nuclei, abundant clear cytoplasm, cytotoxic granules, central nucleoli and villous plasma membrane



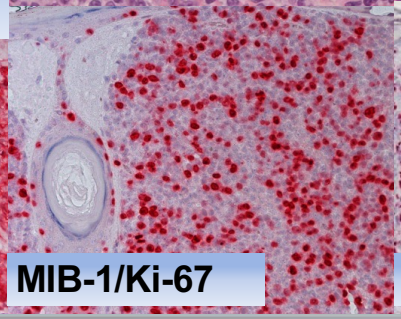




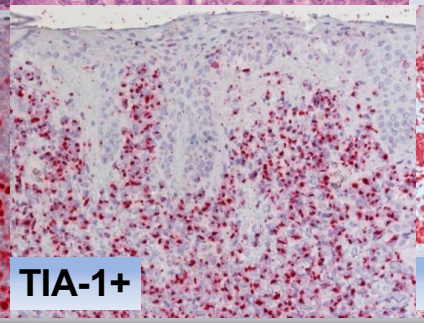
CD3+



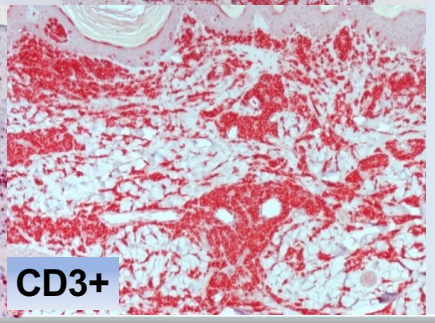
CD45RO+



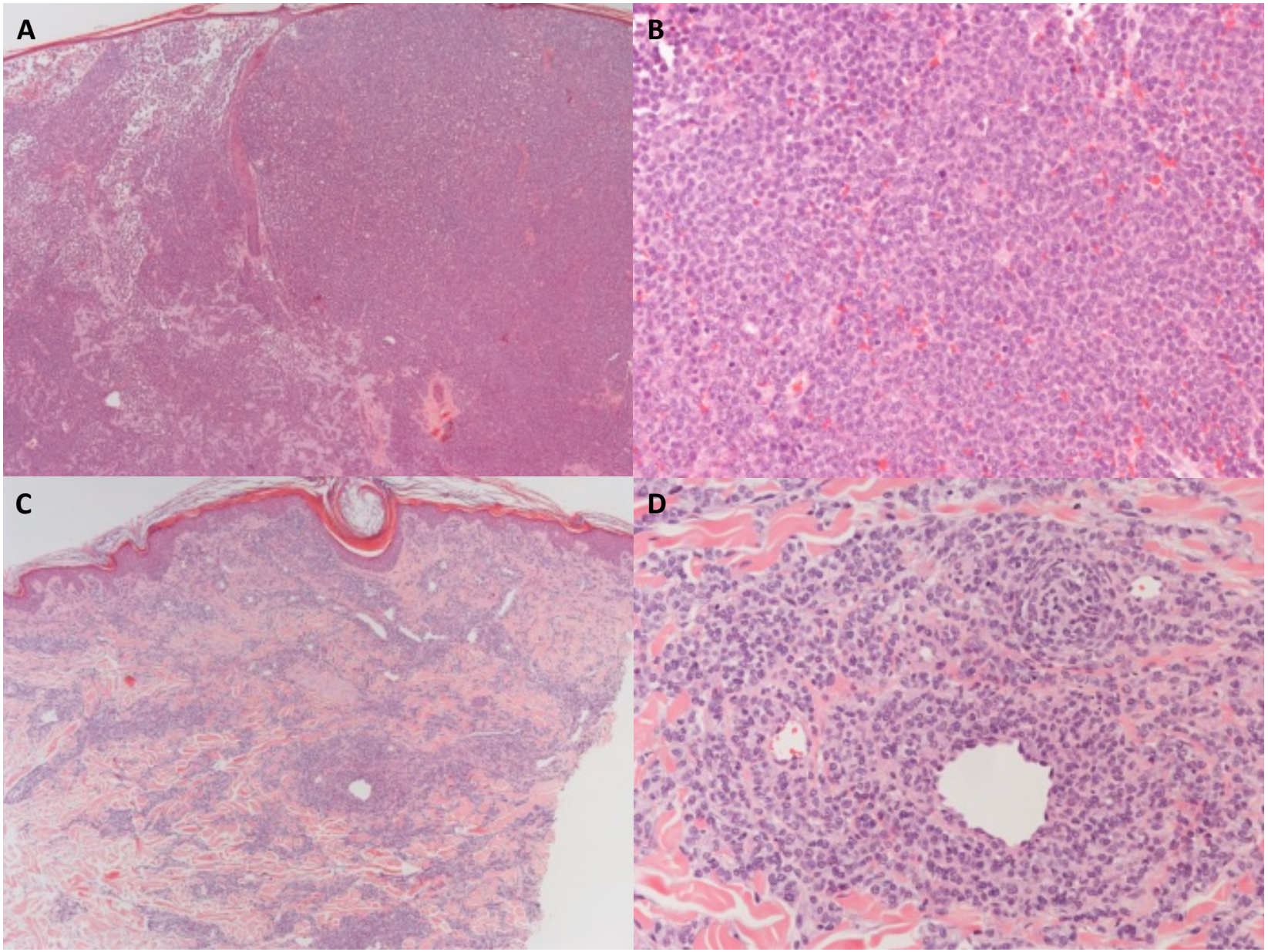
MIB-1/Ki-67



TIA-1+



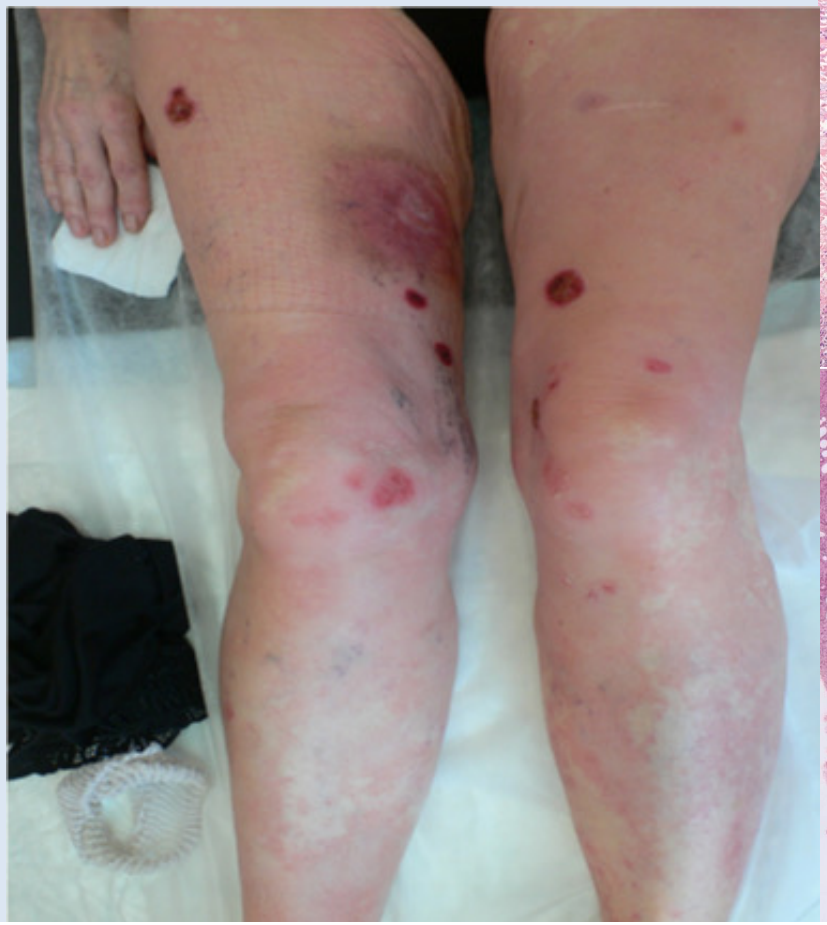
CD3+

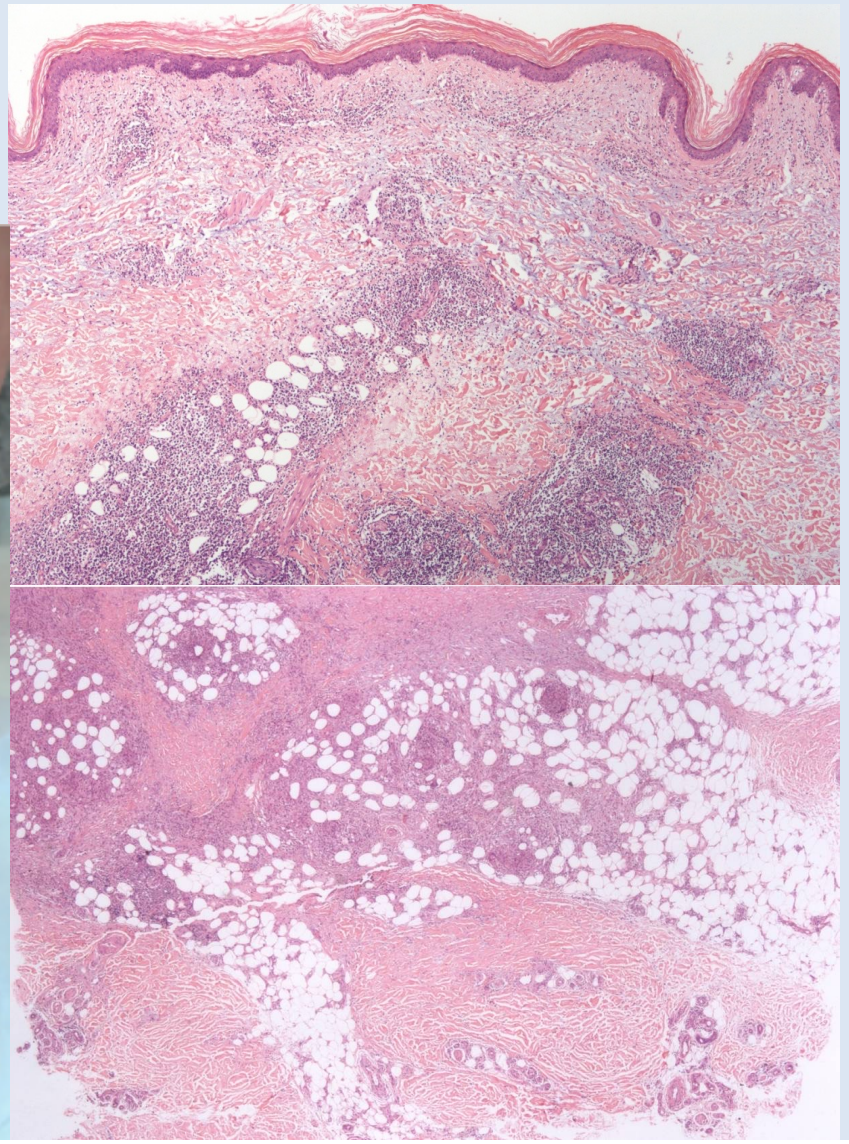

A
B
C
D

Cutaneous Gamma/Delta TCL

- Bad prognosis for all types (epidermotropic, dermal or panniculitic).
- Systemic involvement and no response to conventional Polychemotherapy or Bone Marrow Transplant
- Immunophenotype and evolution similar to those of mucosal gamma/delta TCLs
- CD4-/CD8- cases or CD56+ SPTCL, Beta F1 negative,
  TCR-gamma/delta+

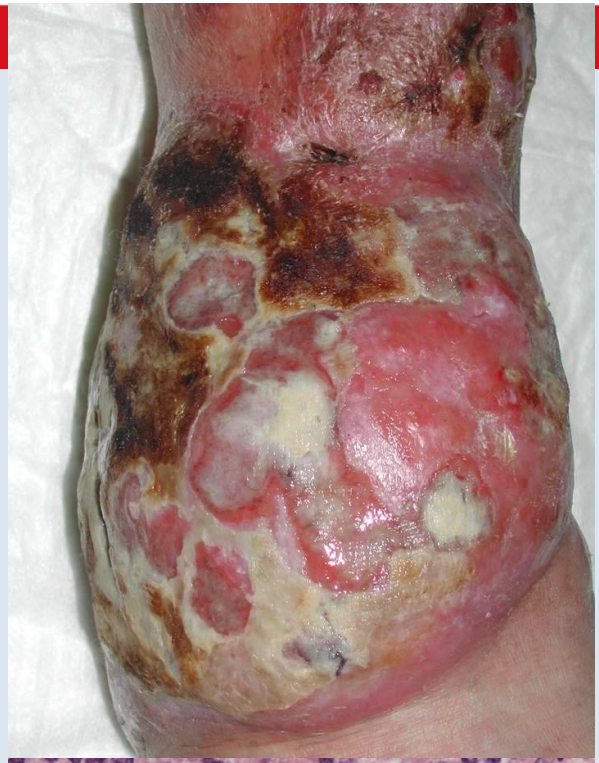
C-GD-TL with SPTCL presentation: the epidermis and dermis are also infiltrated by neoplastic cells.

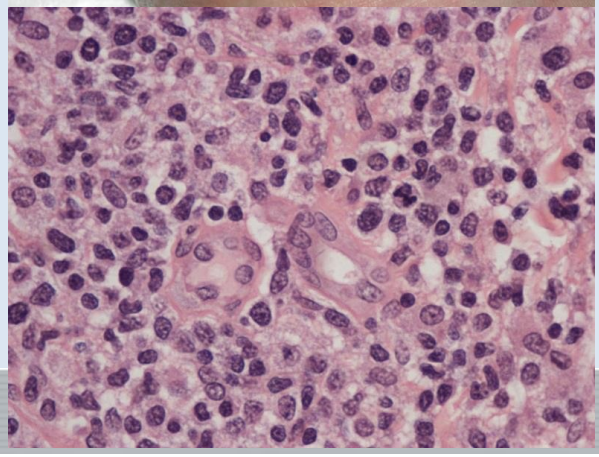




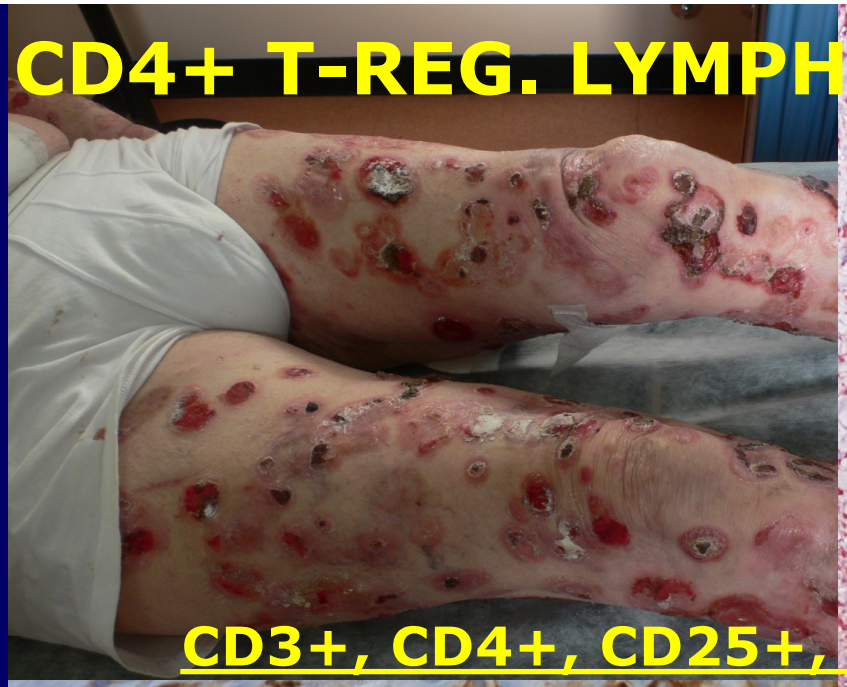
EXTRANODAL PC ENT-NK/T LYMPHOMA (aggressive)

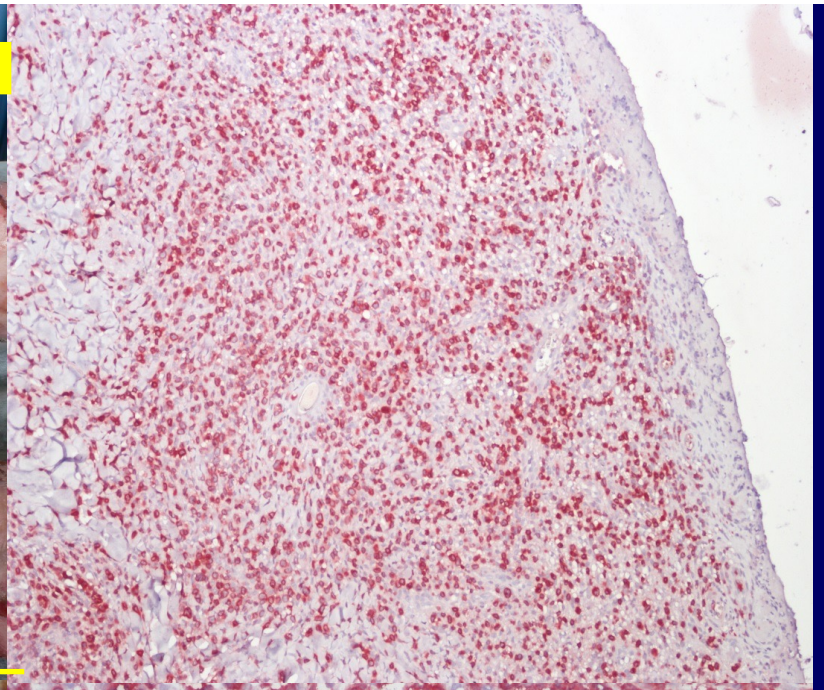
- Rare
- Rapidly disseminated nodulo-tumoral necrotic lesions
- Localization: face,trunk and extremities .
- Immunophenotype: CD2+, CD56+, CD45RO+, surface CD3-, cytoplasmic CD3+.
- **EBV tumor cell integration (EBER1-2+)**
- TCR germline configuration – rare cases with TCR monoclonal rearrangement.
- poor prognosis



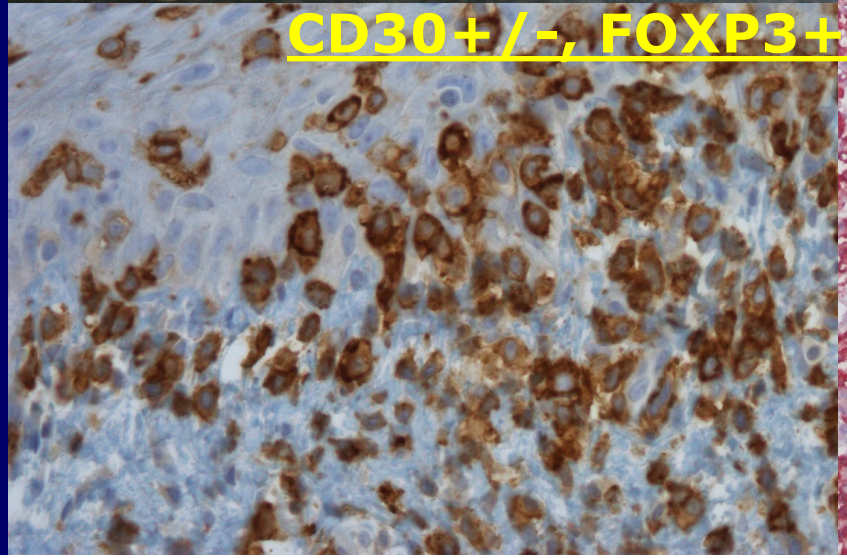


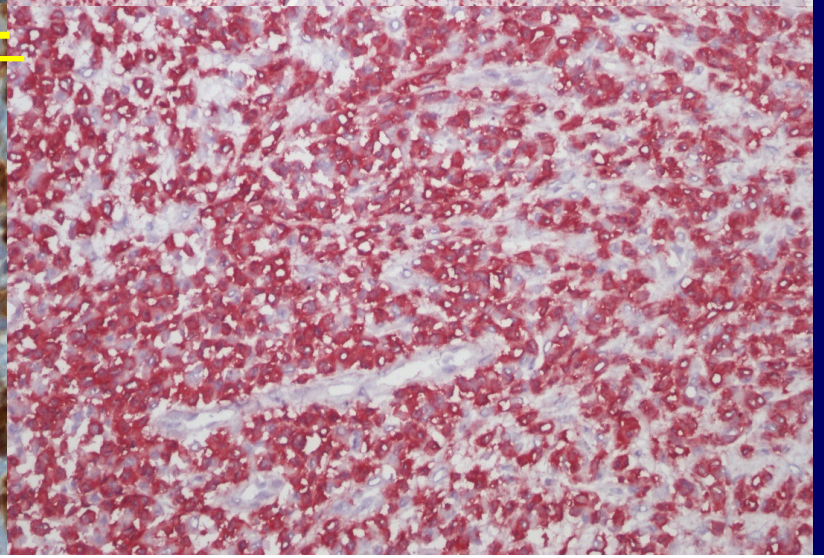
CD4+ T-REG. LYMPH





CD3+, CD4+, CD25+, CD30+/-, FOXP3+

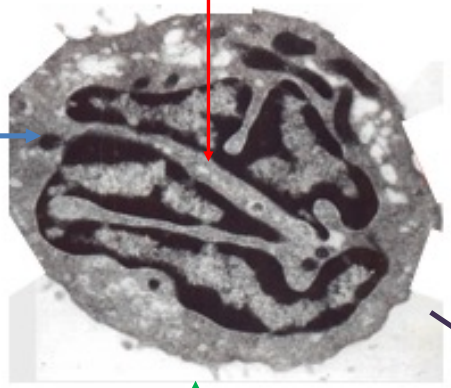


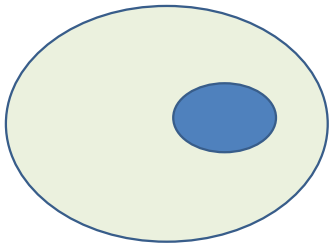


TERAPIA “TARGET” CTCL

NUCLEO
HDAC inhibitors
PNP: forodesine
DNA alkylating: mechlorethamine

PATHWAYS
JAK-STAT inhibitors



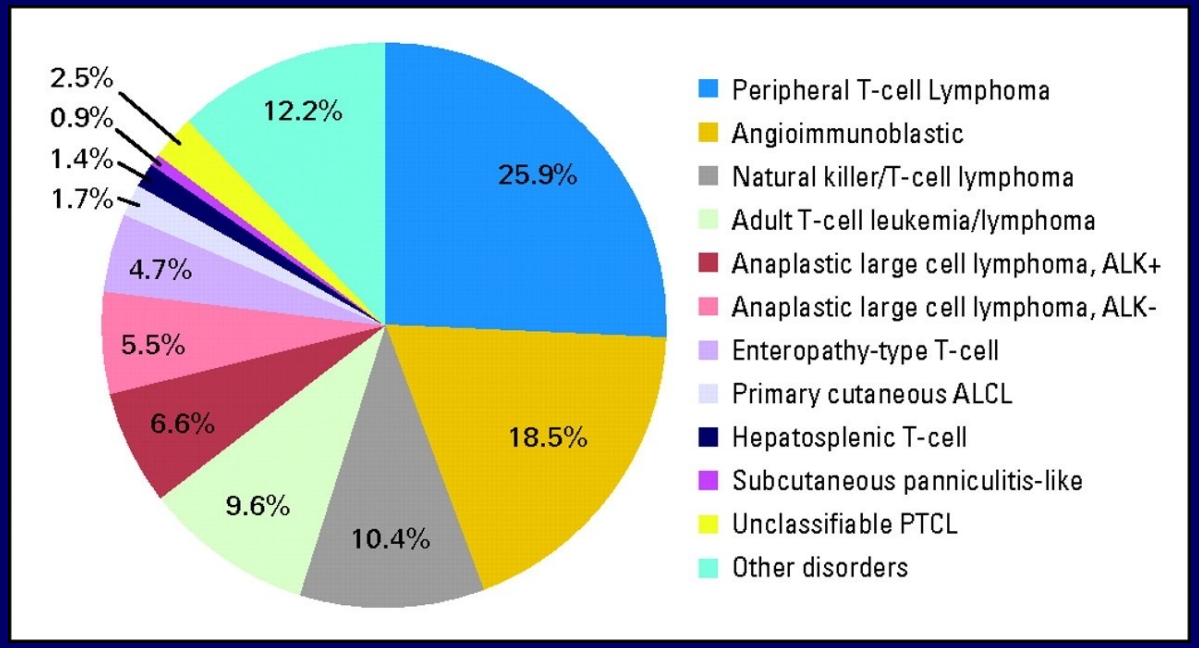


CHECK-POINT INHIBITORS
Anti-PD-1/PDL-1

STEM CELLS
Allo-HSCT

SURFACE MARKERS
CD30: brentuximab vedotin
CCR4: mogamulizumab
CD158k/KIR3DL2: IPH4102

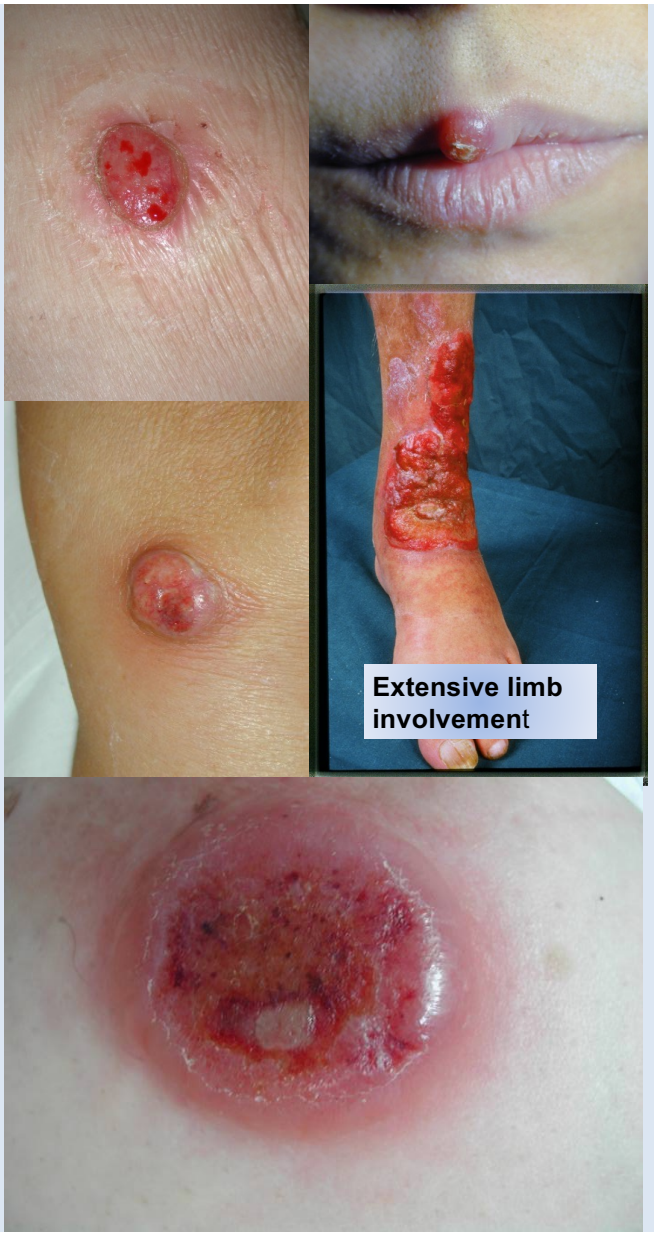
Fig 1. Distribution of 1,314 cases of PTCL by consensus diagnosis



International T-Cell Lymphoma Project, J Clin Oncol; 26:4124-4130 2008

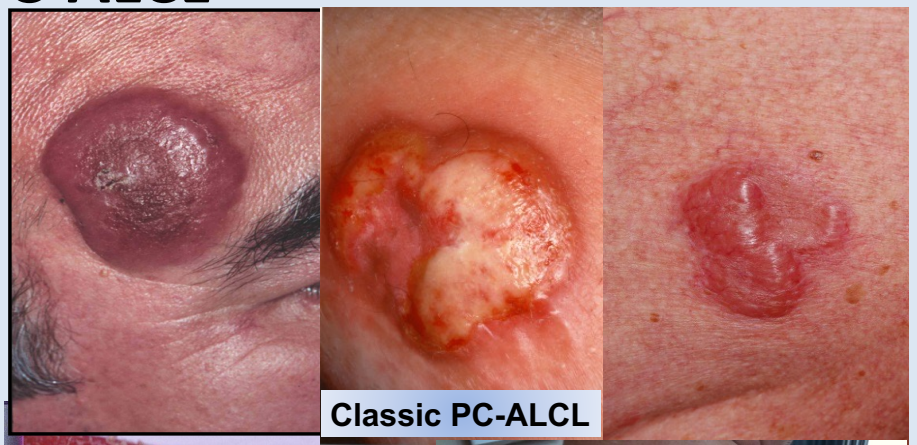
Primary cutaneous CD30 positive large cell lymphoma (PC-ALCL) (INDOLENT)

- 5th and 6th decade of life male/female ratio 3:1
- Rarely in pediatric age.
- No clinical evidence or history of LyP, MF, or another type of CTCL.
- No evidence of nodal and visceral involvement
- (workup studies essential)
- Expression of the CD30 antigen by more than 75% of tumor cells
- Anaplastic lymphoma Kinase (p80) and t(2;5)(p23;q35) negative
- OOS 5Y 95%.

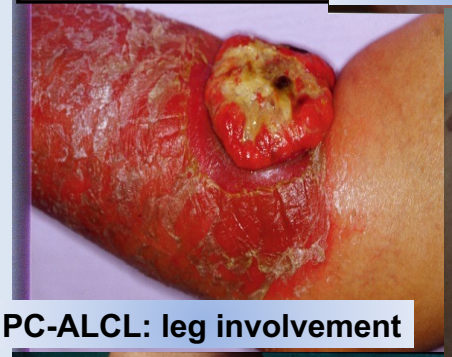


PC-ALCL

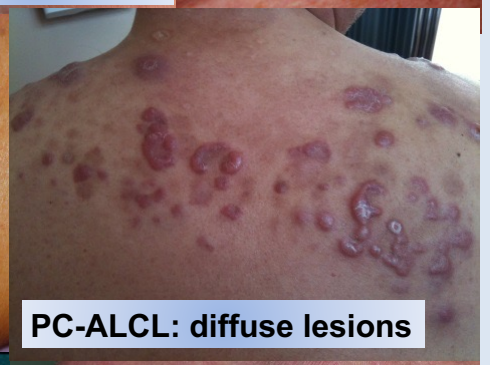
- Solitary, grouped, or multifocal nodular nodulo-tumoral lesions of deep-red colour, with frequent central ulceration.
- Sometimes infiltrative plaques or lesions clinically comparable to the papulo-nodules of LYP or dermo-hypodermal nodules.
- Distribution of lesions is locoregional
- 10% of cases widespread cutaneous involvement.
- Locations: limbs, head, nape, trunk, and genitals.
- 10-20% of cases extensive legs involvement and aggressive course with lymph nodes extension.
- In some cases, PC-ALCL manifests in MF patients or precedes the appearance of a classic MF. If this is the event, it's a sign of MF large cell transformation, and carries a poor prognosis.
- Skin secondarily involved by nodal or visceral CD30+ ALCL: simple clinical observation and ancillary studies do not allow D.D. from Nodal ALCL
- FULL WORKUP STUDIES MUST BE ALWAYS PERFORMED



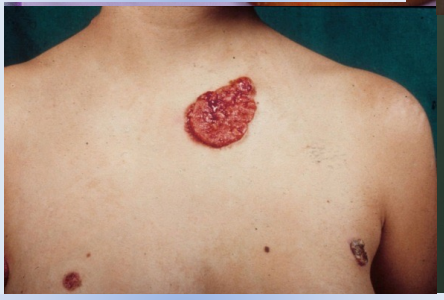
Classic PC-ALCL



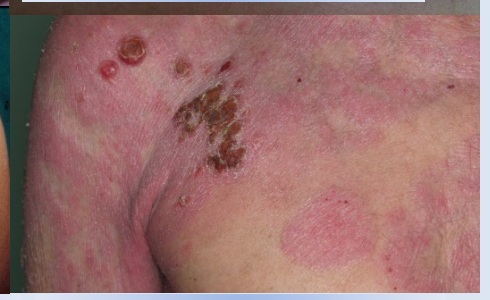
PC-ALCL: leg involvement



PC-ALCL: diffuse lesions

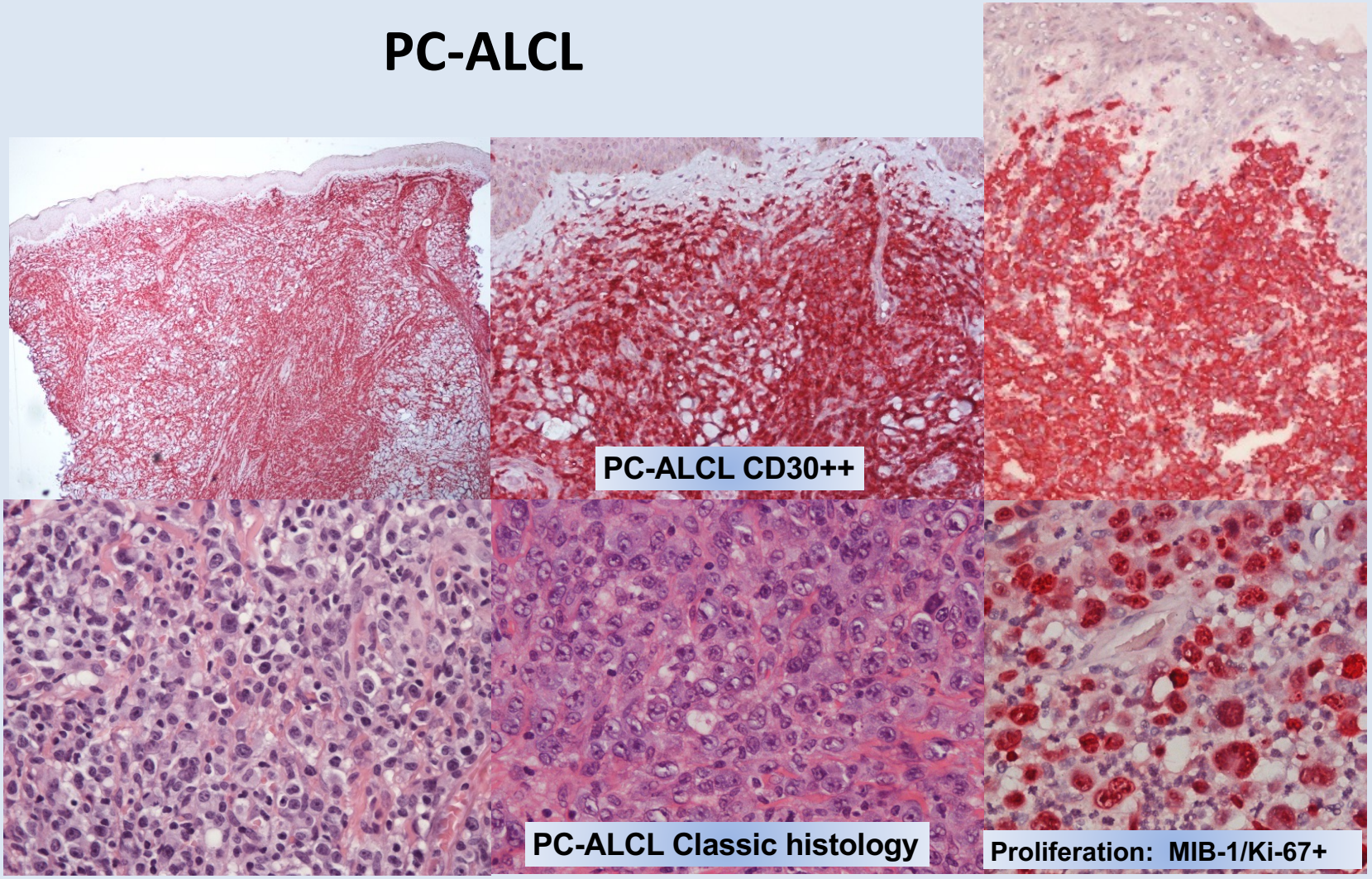


PC-ALCL in a 13 years old female



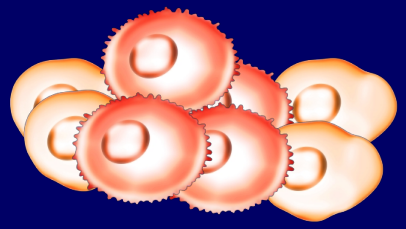
MF/ALCL: CD30+ nodules

PC-ALCL


PC-ALCL CD30++
PC-ALCL Classic histology
Proliferation: MIB-1/Ki-67+

Targeting T-cell Lymphoma

Surface Antigens/Receptors
CD2
CD4
CD25
CD30
Chemokine recepto



Microenvironmental Factors
Angiogenesis
Immunomodulation
Viral Pathogens

Cellular Survival Mechanisms
Proteasome Inhibition
HDAC inhibition
Death Receptors & Ligands
Cell Cycle Arrest
Signal Transduction Inhibition

Novel Agents: MoAbs for the Treatment of PTCL

MoAb	Target	Notes
MDX-060	CD30	Fully human IgG1
SGN-30	CD30	Chimeric murine/human antibody
Brentuximab vedotin (SGN-35)	CD30	SGN-30 fused with antitubulin agent
Zanolimumab	CD4	IgG1 ; targets T-helper cells
Alemtuzumab	CD52	IgG1; CD52 highly expressed on malignant T cells
KW-0761	CCR4	Defucosylated humanized IgG1

MoAb=monoclonal antibody.

Ansell. *J Clin Oncol.* 2007;25:2764; Pro. *2009 ASCO Educational Book.* Alexandria, VA: American Society of Clinical Oncology. 2009;486; Enblad. *Blood.* 2004;103:2920; Yamamoto. *ASH.* 2008 (abstr 1007).

BIOMARKERS DI SUPERFICIE

- ***Syndecan 4***
  - Over-espresso nella SS → DD con altre leucemie e dermatiti infiammatorie
- ***Sialomucina (CD164)***
  - Over-espressione nella SS
  - Correlazione inversa tra CD164 e CD26 → marker per diagnosi, prognosi e staging
- ***CCR4***
  - Normalmente espresso dalle TH2 e Treg e promuove la migrazione delle cellule T nella pelle dopo il legame con i suoi ligandi (CCL17 e CCL22)
  - tMF e SS hanno un'espressione significativamente maggiore di CLA e CCR4 sulle cellule della cute e del sangue rispetto alle cellule sane
  - Target terapeutico (Mogamulizumab)

Ferenczi K, et al. J invest Dermatol 2002;119:1405

Mogamulizumab vs Vorinostat in Previously Treated Pts With CTCL (MAVORIC): Background

- Pts with CTCL have poor quality of life due to severe itching and recurrent skin infections[1]
- Mogamulizumab: defucosylated humanized monoclonal antibody directed against CCR4 [2,3]
  - CCR4 overexpressed on malignant T cells in CTCL[4]
  - Mogamulizumab demonstrated tolerable safety profile and 37% ORR in pts with CTCL in phase I/II trial[4]
  - Approved in Japan for CCR4+ R/R ATL, PTCL, and CTCL[5,6]
- Current phase III study sought to evaluate efficacy and safety of mogamulizumab vs vorinostat in pts with previously treated CTCL[7]

References in slidenotes

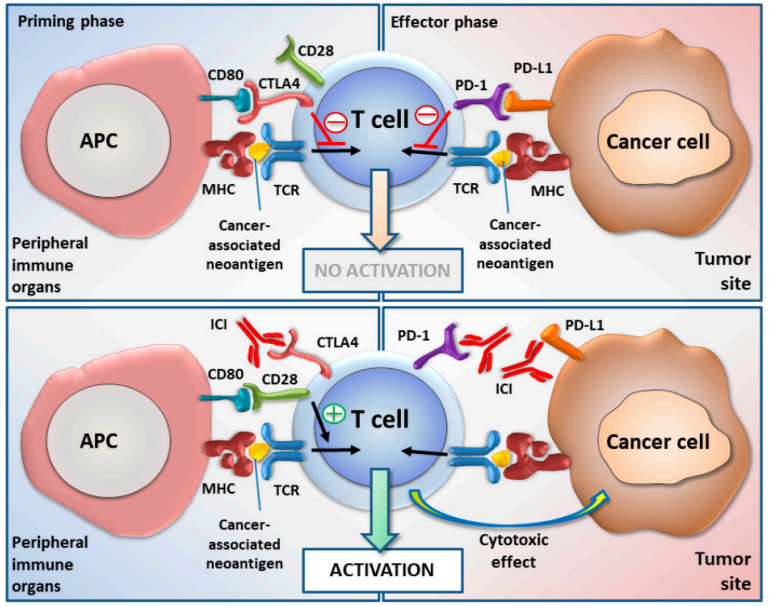
BIOMARKERS DI SUPERFICIE

- ***KIR3DL2/CD158k***
  - Killer-cell immunoglobulin-like receptor
  - Espresso dalle NK e dalle cellule di Sézary
  - Importanza per **diagnosi** e **follow-up** della SS
  - valutazione del tumor burden
  - Diagnosi differenziali con dermatiti infiammatorie, soprattutto nelle forme di SS iniziale che non rispecchia ancora i criteri diagnostici
  - Therapeutic target (IPH4102)
  - Evidenza di eterogeneicità delle KIR3DL2+SC che mostrano una diversa maturazione tra sangue e pelle

Hurabielle C, et al. Clin Cancer Res 2017.
Roelens M, et al. Blood 2017;130:1468

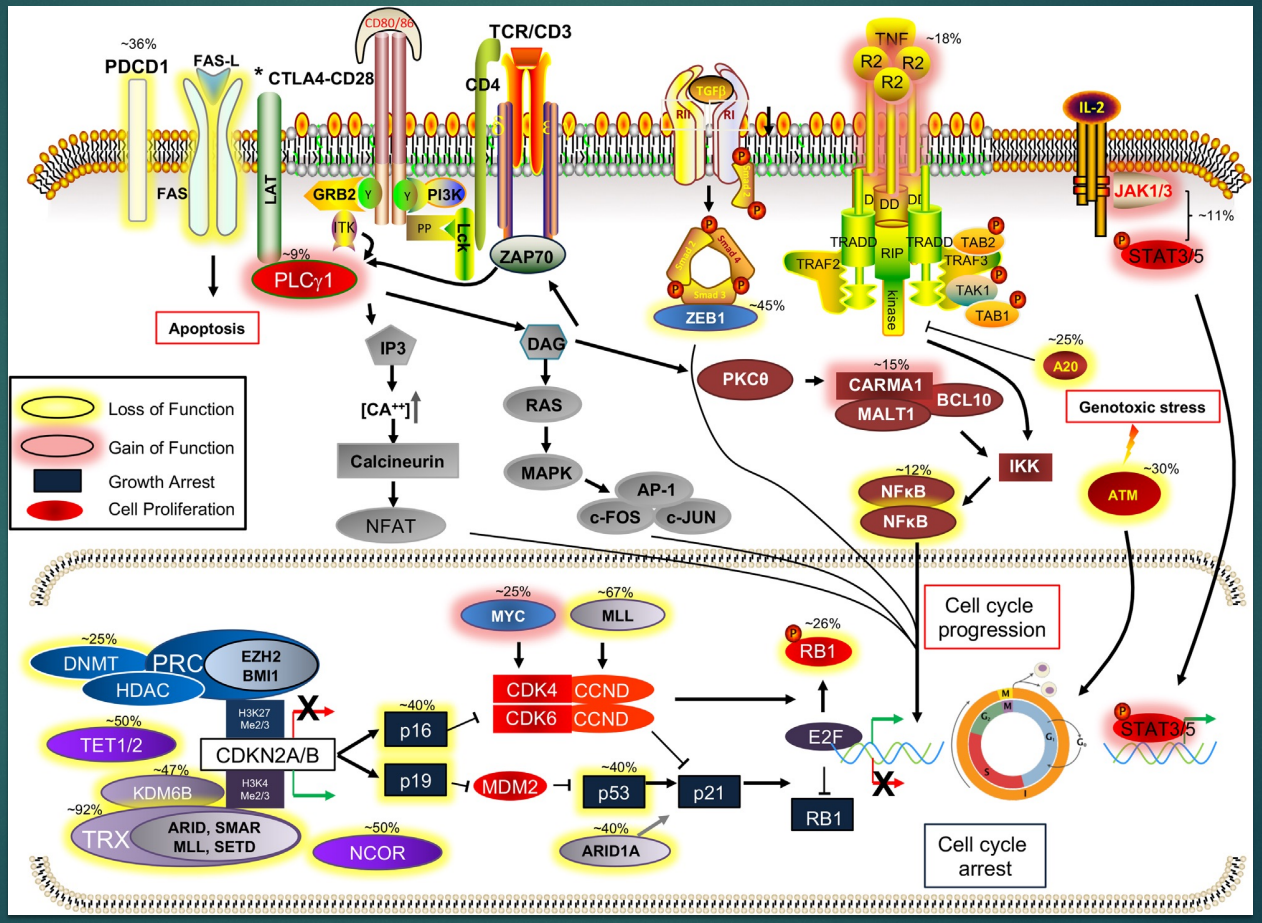
BIOMARKERS DI SUPERFICIE

- ***PD1***
  - Gioca un ruolo regolatorio del sistema immunitario promuovendo l'immunotolleranza
  - Espresso dalle cellule T, inibisce la proliferazione T cellulare mediata dal TCR
  - È parte di un nuovo gruppo di immune-checkpoint che promuovono l'apoptosi delle cellule T antigene specifiche e inibiscono l'apoptosi di quelle regolatorie
  - Over-espressione nella SS >>> MF
  - Target terapeutico
- ***CTLA-4***
  - T cell surface protein
  - Overespressione del gene di fusione CTLA4-CD28 nella SS e MF
  - Target terapeutico



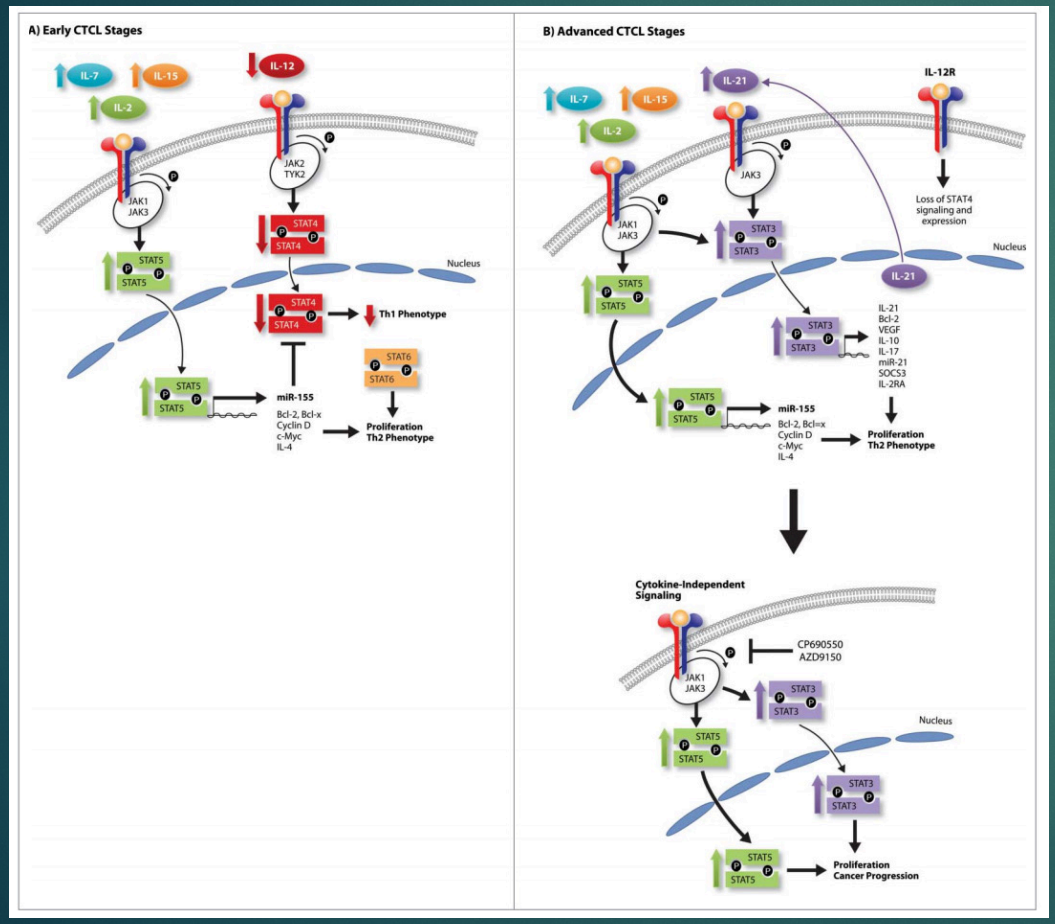
Cristofoletti C, et al. Chin Clin Oncol 2019;8(1):2
Bobrowicz M, et al. Cancer 2019;11:1420

MF/SS – genomic landscape

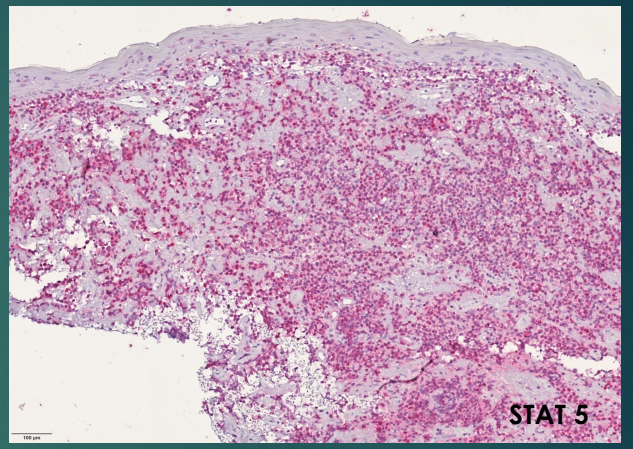


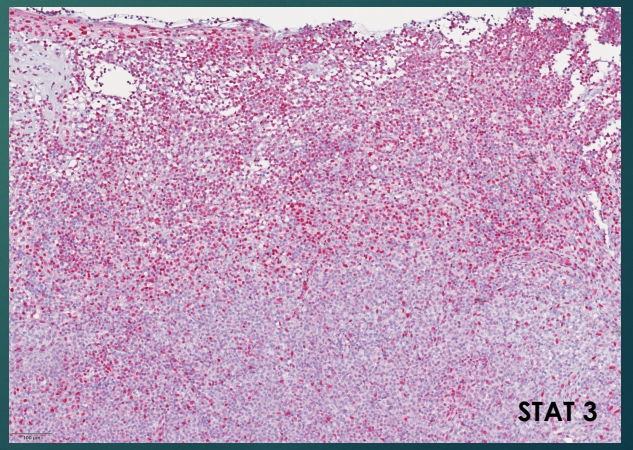
K.S.J. Elenitoba. Seminars in Diagnostic Pathology 34 (2017) 15–21

JAK/STAT signaling changes in CTCL



Netchiporouk et al, 2014





EPIGENETIC BIOMARKERS - MIRNA

22 pts

Citation: Cell Death and Disease (2011) 2, e151; doi:10.1038/cddis.2011.32

www.nature.com/cddis

MicroRNA profiling reveals that miR-21, miR486 and miR-214 are upregulated and involved in cell survival in Sézary syndrome

MG Narducci[1], D Arcelli[1], MC Picchio[1], C Lazzeri[1], E Pagani[1], F Sampogna[1], E Scala[1], P Fadda[1], C Cristofoletti[1], A Facchiano[1], M Frontani[1], A Monopoli[1], M Ferracin[2], M Negrini[2], GA Lombardo[1], E Caprini[1] and G Russo*[,1]

21 pts

blood
2010 116: 1105-1113
Prepublished online May 6, 2010;
doi:10.1182/blood-2009-12-256719

MicroRNA expression in Sézary syndrome: identification, function, and diagnostic potential

Erica Ballabio, Tracey Mitchell, Marloes S. van Kester, Stephen Taylor, Heather M. Dunlop, Jianxiang Chi, Isabella Tosi, Maarten H. Vermeer, Daniela Tramonti, Nigel J. Saunders, Jacqueline Boultwood, James S. Wainscoat, Francesco Pezzella, Sean J. Whittaker, Cornelius P. Tensen, Christian S. R. Hatton and Charles H. Lawrie

Y Qin et al.
MicroRNA Deep Sequencing of Sézary Syndrome

Deep-Sequencing Analysis Reveals that the miR-199a2/214 Cluster within DNM3os Represents the Vast Majority of Aberrantly Expressed MicroRNAs in Sézary Syndrome

Journal of Investigative Dermatology (2012) **132,** 1520–1522; doi:10.1038/jid.2011.481; published online 16 February 2012

J Eur Acad Dermatol Venereol. 2017 Jan;31(1):e27-e29. doi: 10.1111/jdv.13597. Epub 2016 Mar 3.

miR-155 expression in Primary Cutaneous T-Cell Lymphomas (CTCL).

Fava P[1], Bergallo M[2], Astrua C[1], Brizio M[1], Galliano I[2], Montanari P[2], Daprà V[2], Novelli M[1], Savoia P[1], Quaglino P[1], Fierro MT[1].

UP: **miR-199a**; **miR-214**; **miR-486**; **miR-21**, **miR-155**
DOWN: **miR-31**; **miR-125b**