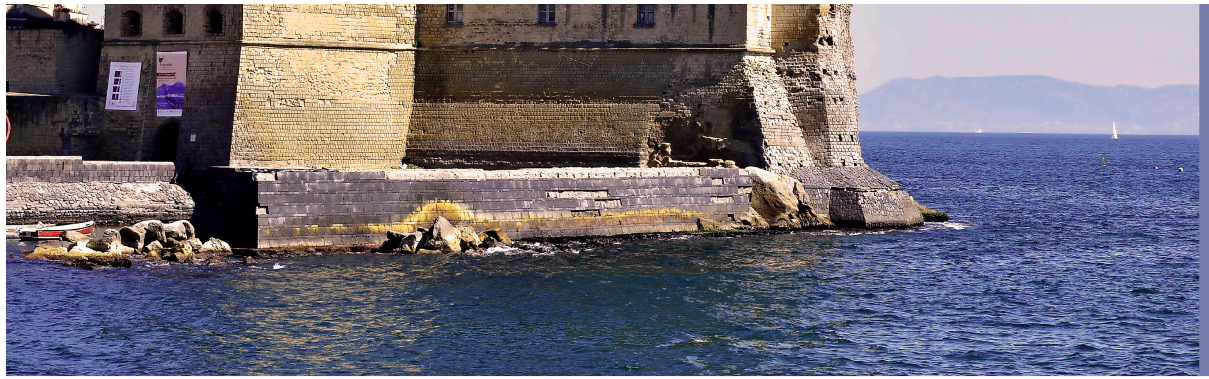


T-LINFOCITARIA:

la multidisciplinarità ottimizza il risultato

29 OTTOBRE 2021

NAPOLI Hotel Royal Continental

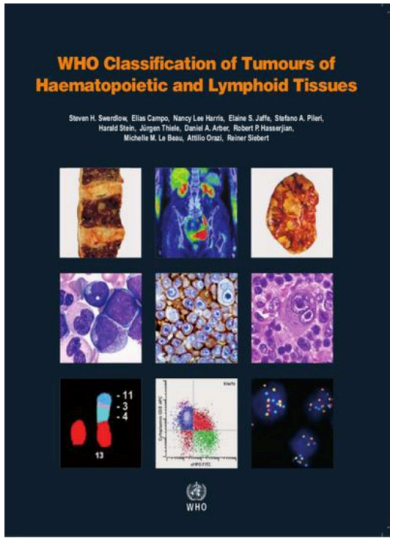
L'Identikit dei linfociti circolanti

- E. Berti, S. Alberti-Violetti

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

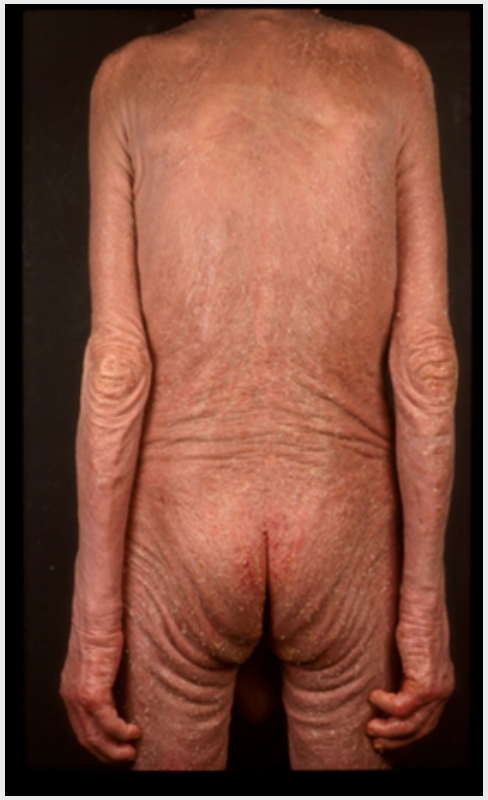
- Nessun conflitto d'interesse in relazione alla presentazione odierna

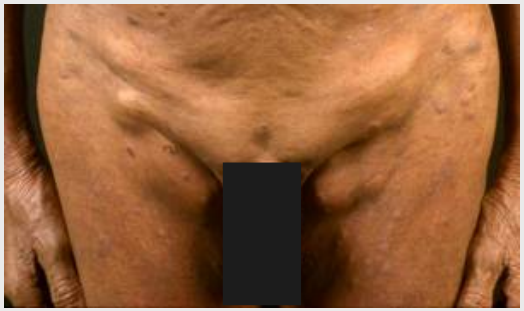
Updated 4° edition of WHO classification

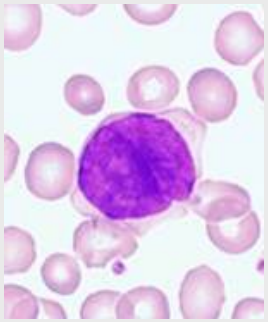


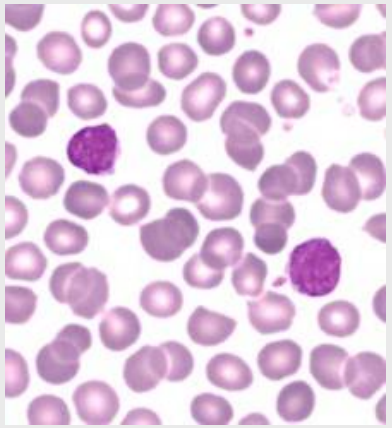
WHO-EORTC Classification 2018	Frequency, %*	5-y DSS, %*
CTCL		
MF	39	88
MF variants		
Folliculotropic MF	5	75
Pagetoid reticulosis	<1	100
Granulomatous slack skin	<1	100
SS	2	36
Adult T-cell leukemia/lymphoma	<1	NDA
Primary cutaneous CD30$^+$ LPDs		
C-ALCL	8	95
LyP	12	99
Subcutaneous panniculitis-like 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

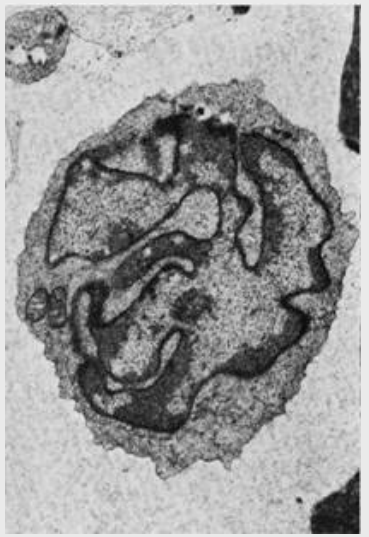
SINDROME DI SEZARY









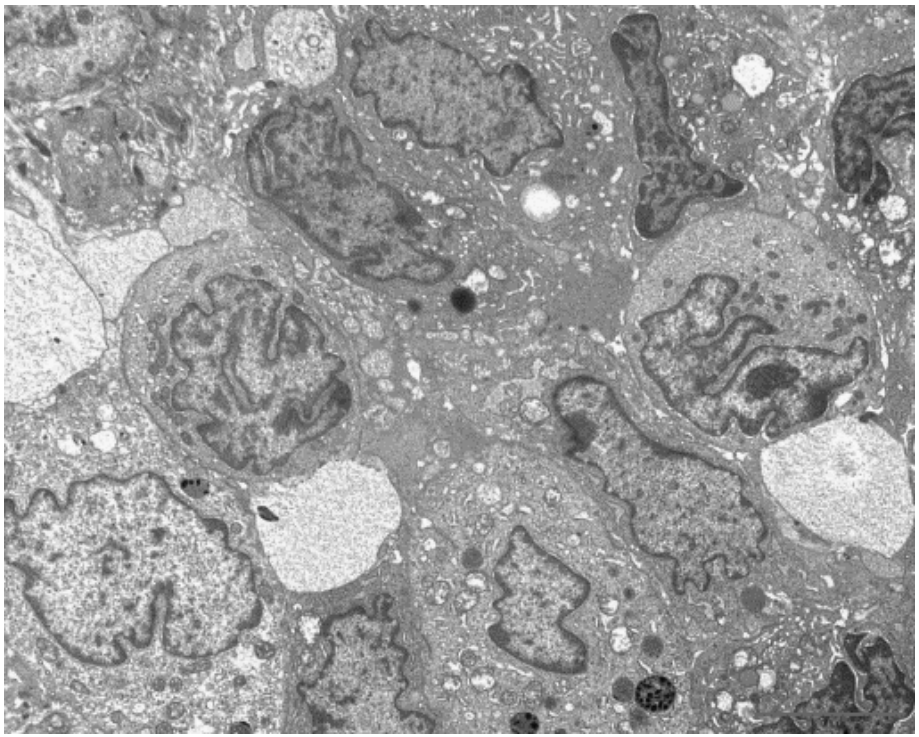


Sézary A, Bouvrain Y : Erytrodermie avec présence de cellules monstrueuses dans le derme et dans le sang circulant . 1938; Bull Soc Fr Derm Symph 45:254.

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

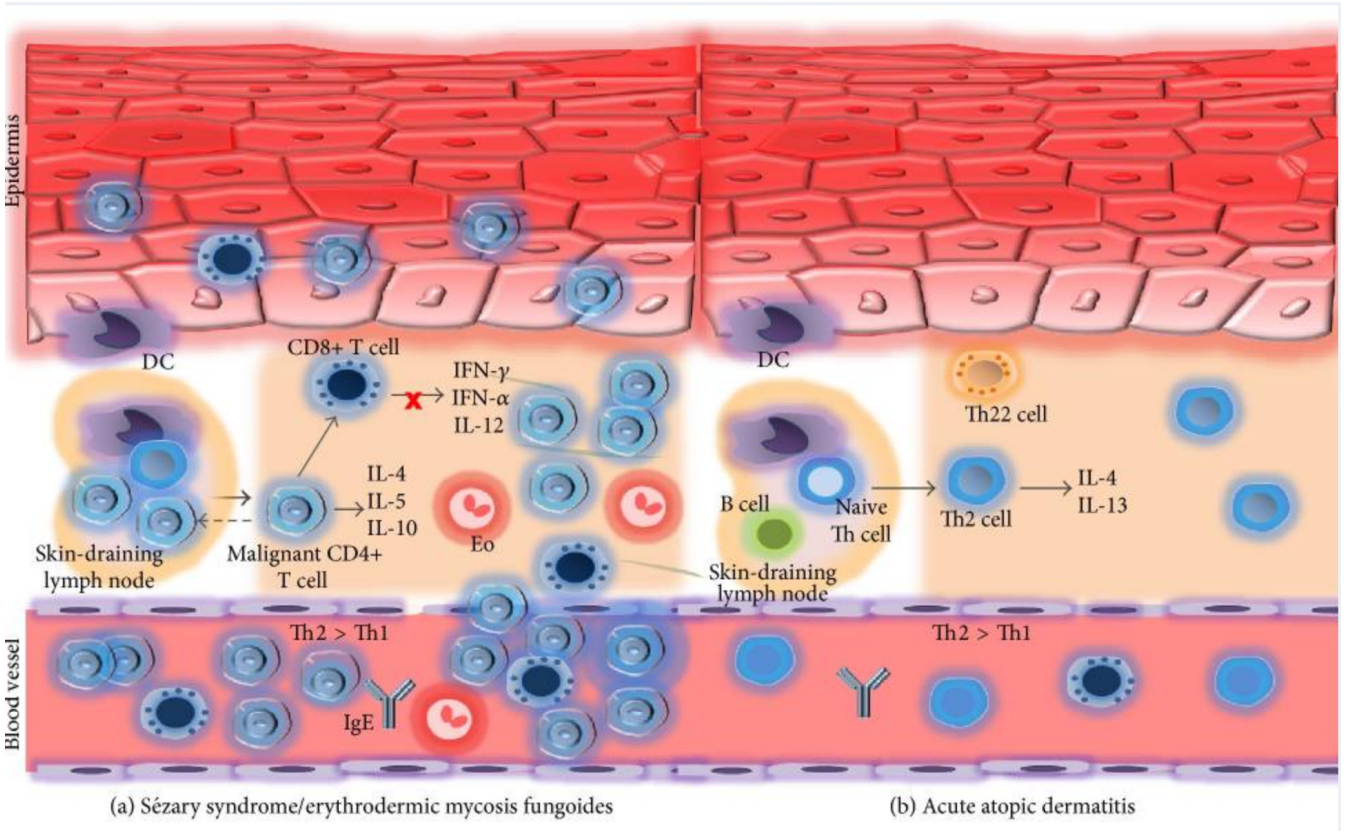
MYCOSIS FUNGOIDES

- 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

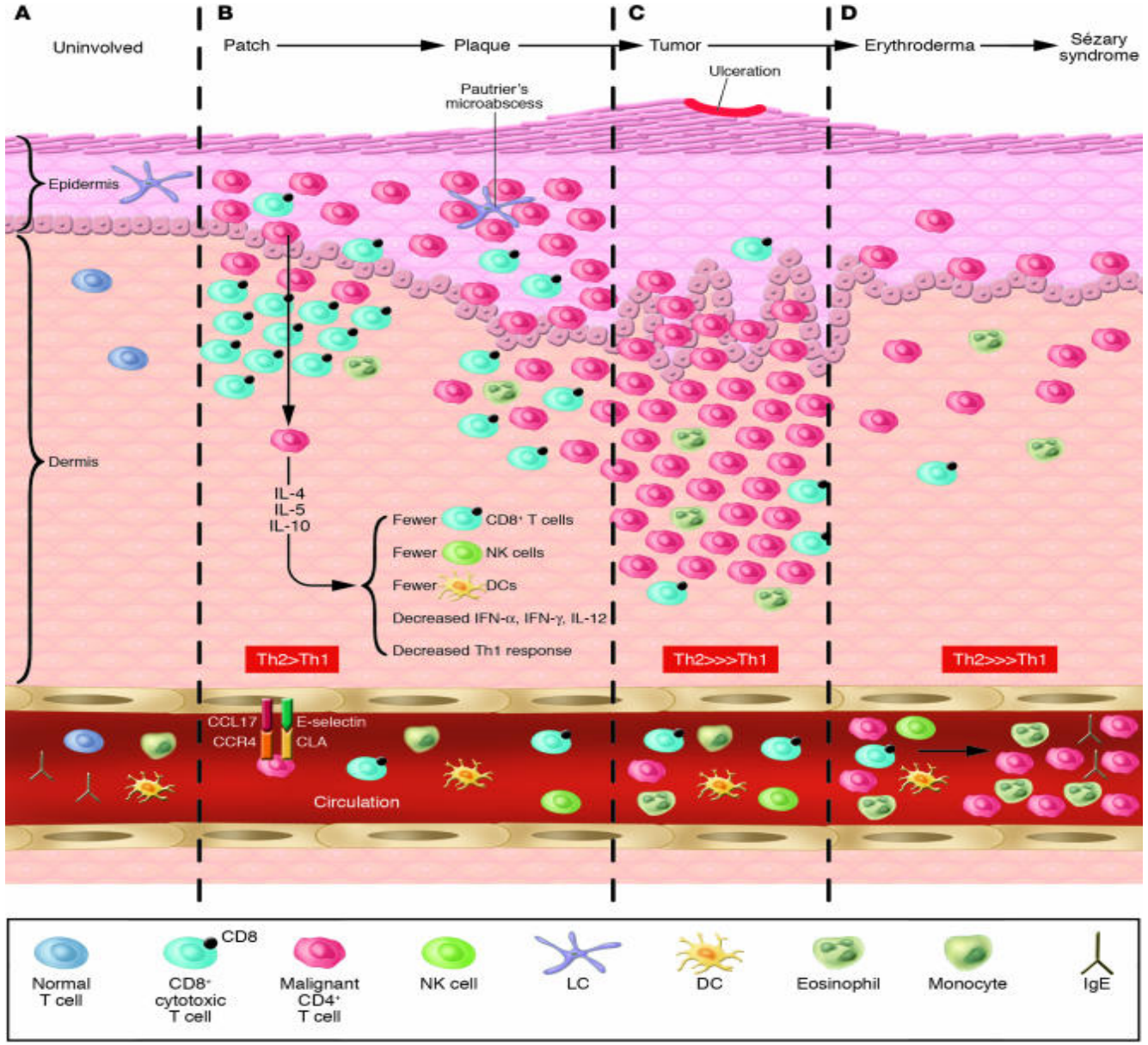


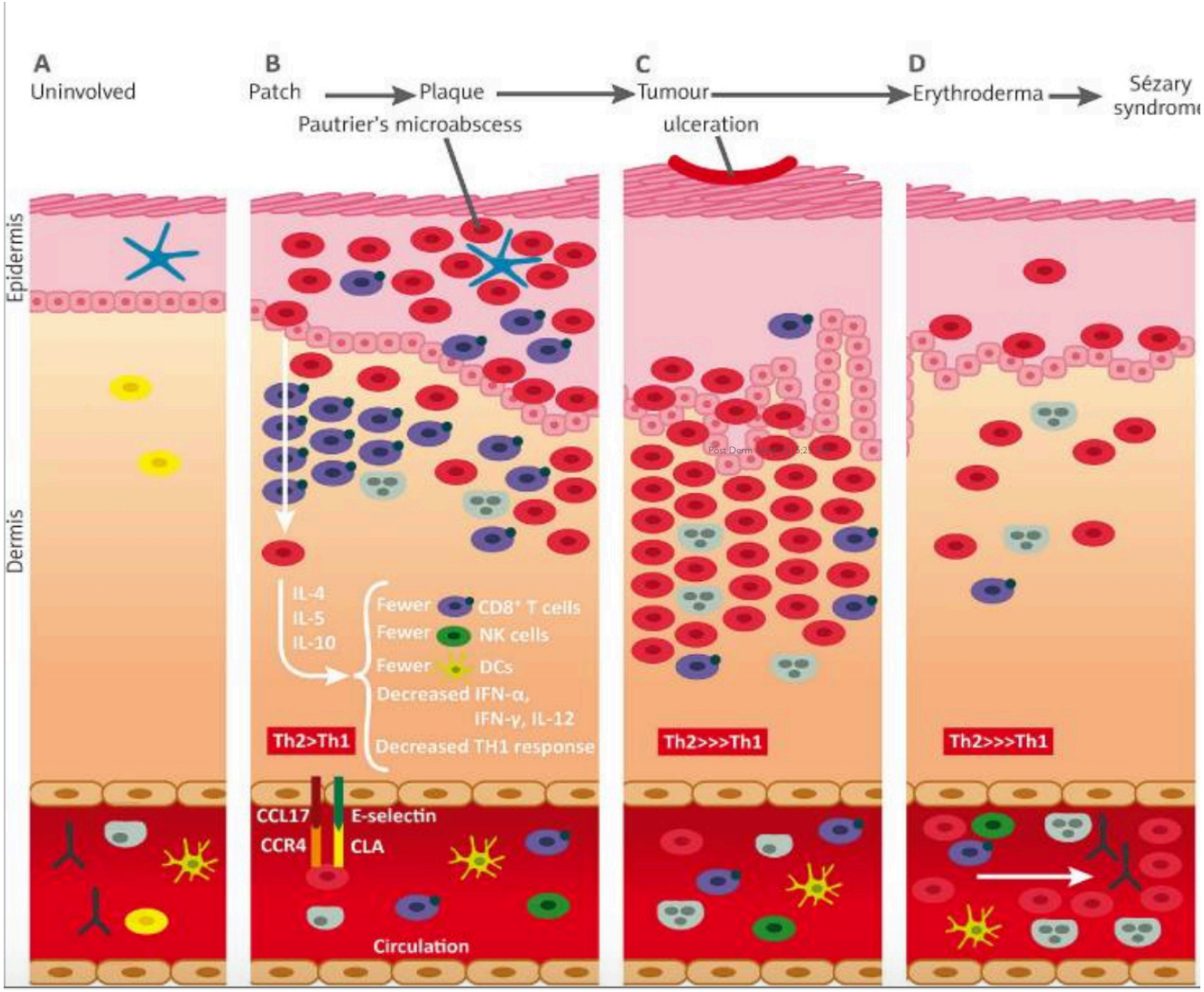
Cerebriform cells

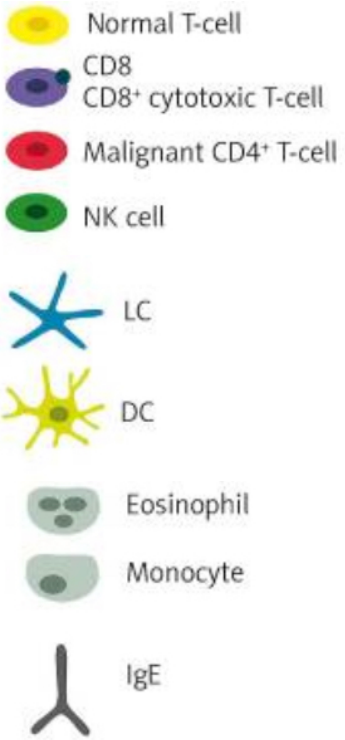
Leukemic CTCL (SS and eMF) and acute AD have both predominance of Th2 immune response



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


A
Uninvolved
B
Patch
Plaque
C
Tumor
D
Erythroderma
Sézary syndrome
Ulceration
Pautrier's microabscess
Epidermis
Dermis
IL-4
IL-5
IL-10
Fewer CD8+ T cells
Fewer NK cells
Fewer DCs
Decreased IFN-α, IFN-γ, IL-12
Decreased Th1 response
Th2>Th1
Th2>>>Th1
Th2>>>Th1
CCL17
CCR4
E-selectin
CLA
Circulation
CD8
Normal T cell
CD8+ cytotoxic T cell
Malignant CD4+ T cell
NK cell
LC
DC
Eosinophil
Monocyte
IgE

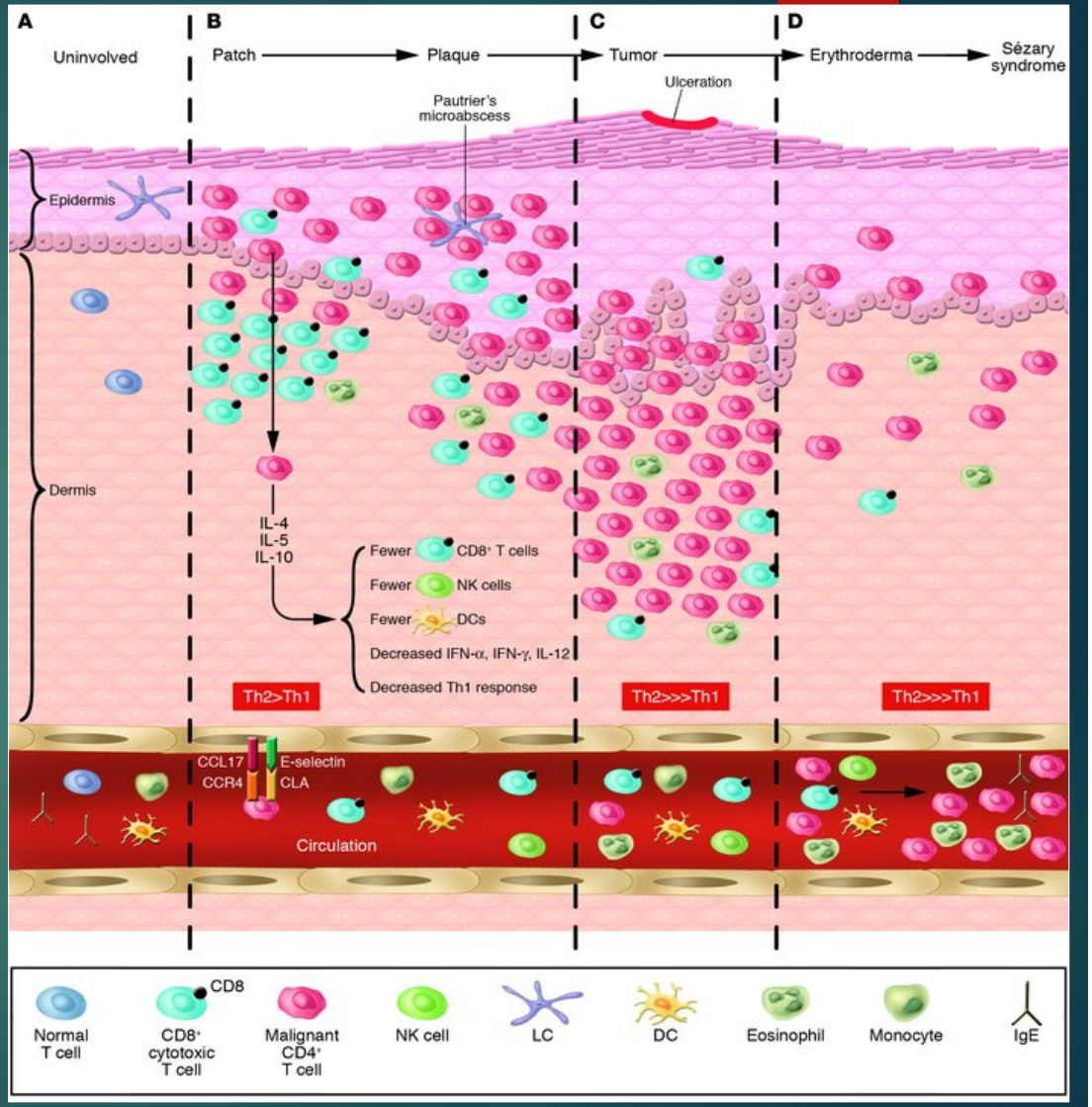




Post Derm Alerg 2015;23:368

MF/SS microenvironment

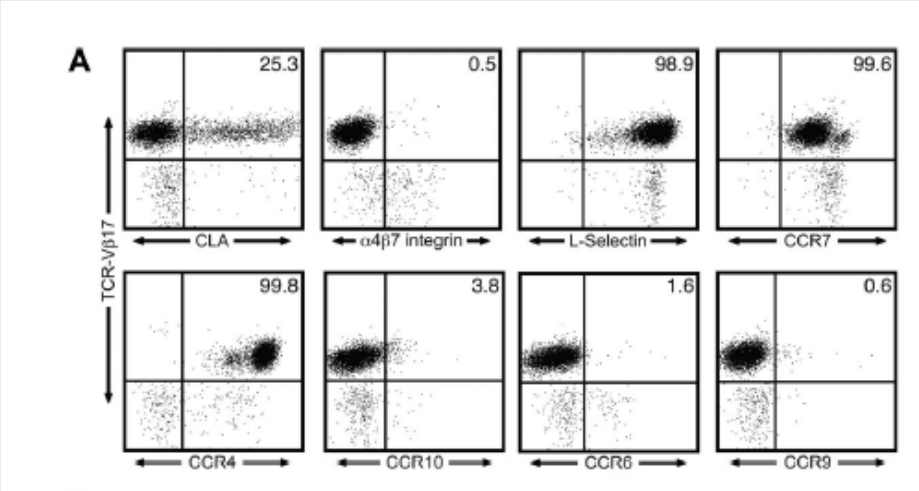
- Early MF
  - Th1 profile
  - IL2, IFNγ , Tbet
  - antitumor immune response
- Advanced MF/SS
  - Th2 profile
  - IL4, IL5, IL10 , GATA3
  - immune failure

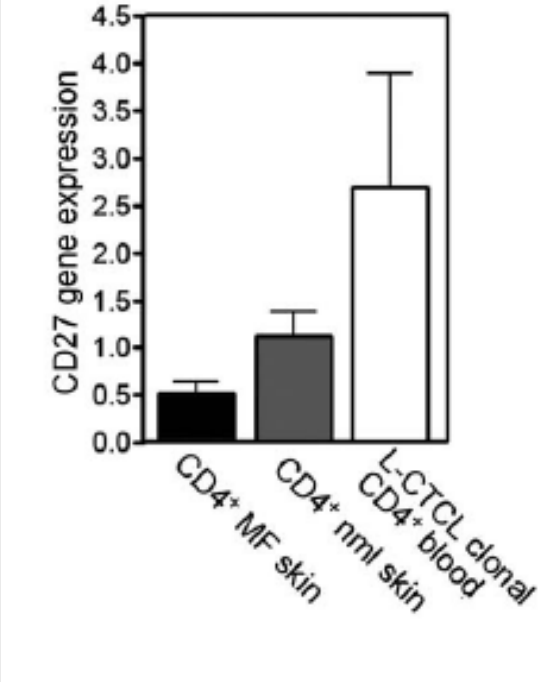


Kim EJ.et al. J Clin Invest. 2005;115(4):798-812

T Naive	CD45RA+ CCR7+CD62L+ CD27+CD28+	Not encounter antigen, self-renewing, homing to secondary lymphoid tissues
TCM	CD45RO+ CCR7+CD62L+ CD27+CD28+	Encounter antigen, self-renewing, homing to secondary lymphoid tissues
TEM	CD45RO+ CCR7-CD62L- CD27+CD28+	Migrating to site of inflammation
T-ERMA	CD45RA+ CCR7-CD62L- CD27-CD28-	Cytotoxic function

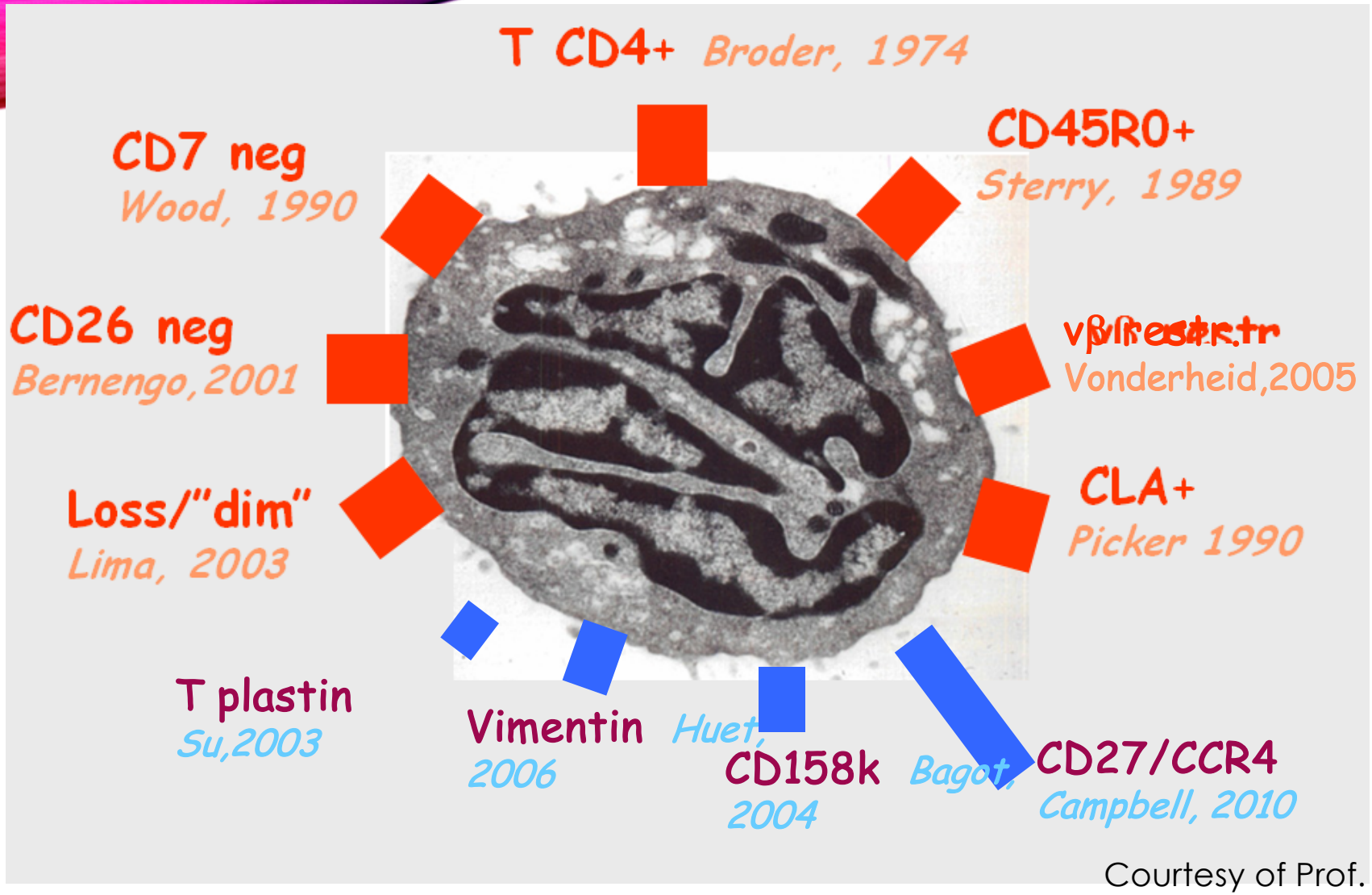
SS: central memory phenotype



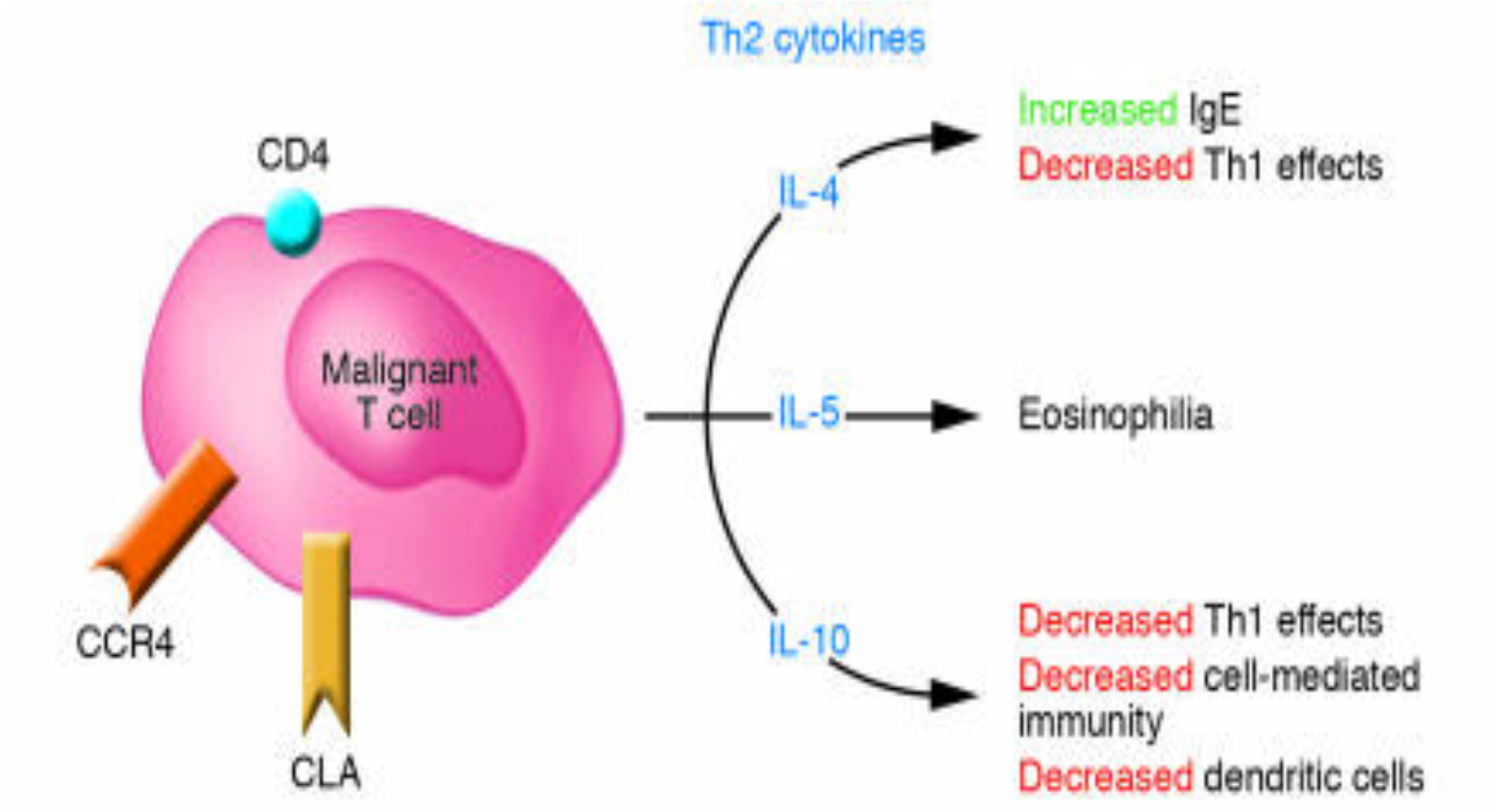


CCR7+CD62L+CD27+

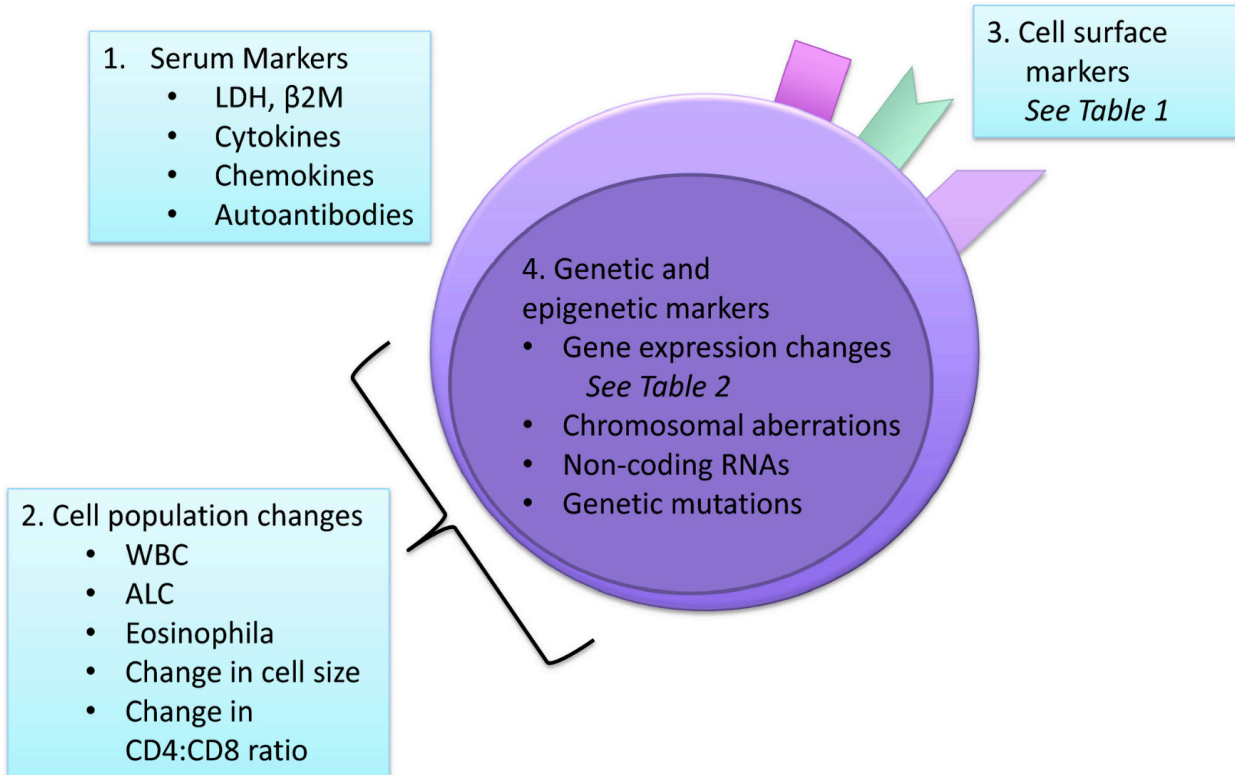
Campbell et al. Blood 2010



Courtesy of Prof. Quaglino


Th2 cytokines
CD4
Malignant
T cell
CCR4
CLA
IL-4
IL-5
IL-10
Increased IgE
Decreased Th1 effects
Eosinophilia
Decreased Th1 effects
Decreased cell-mediated
immunity
Decreased dendritic cells

BIOMARKERS IN MF AND SS



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

MF/SS - Phenotype

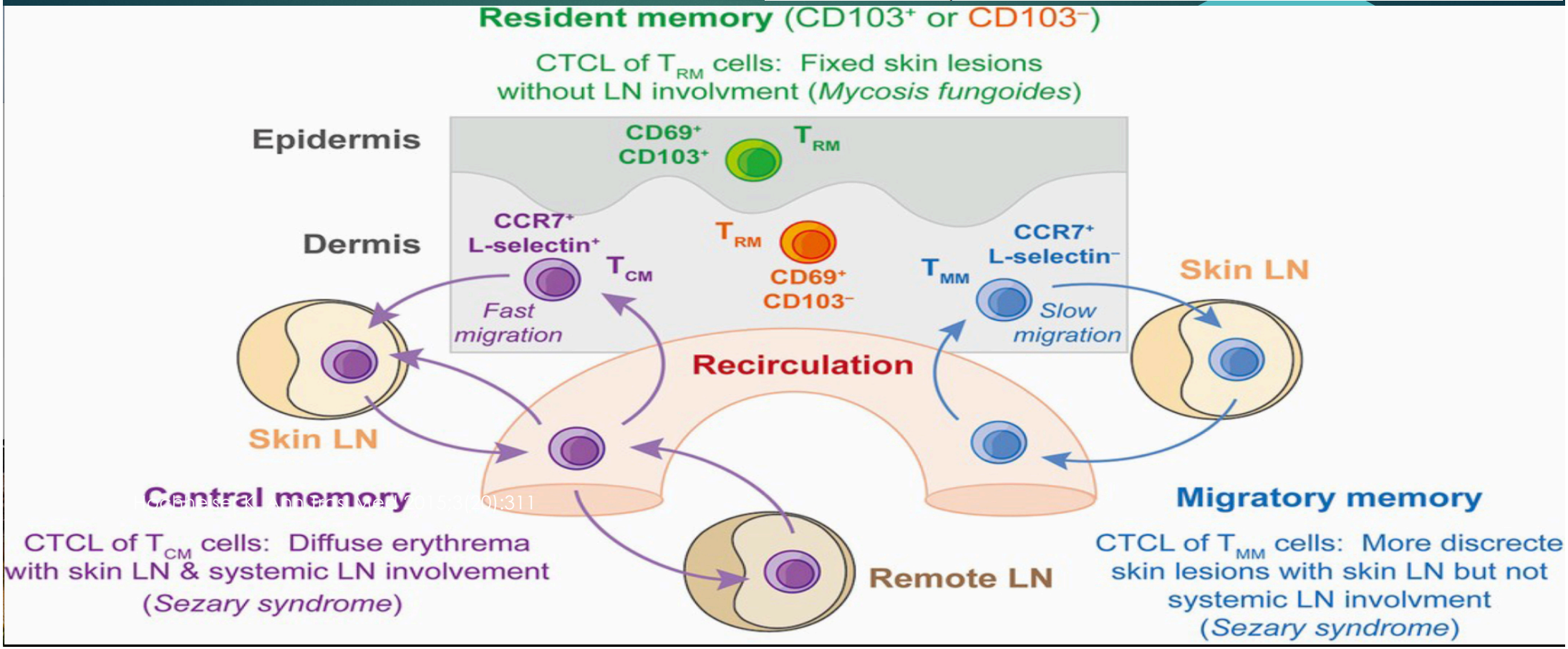
«cell origin» theory

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

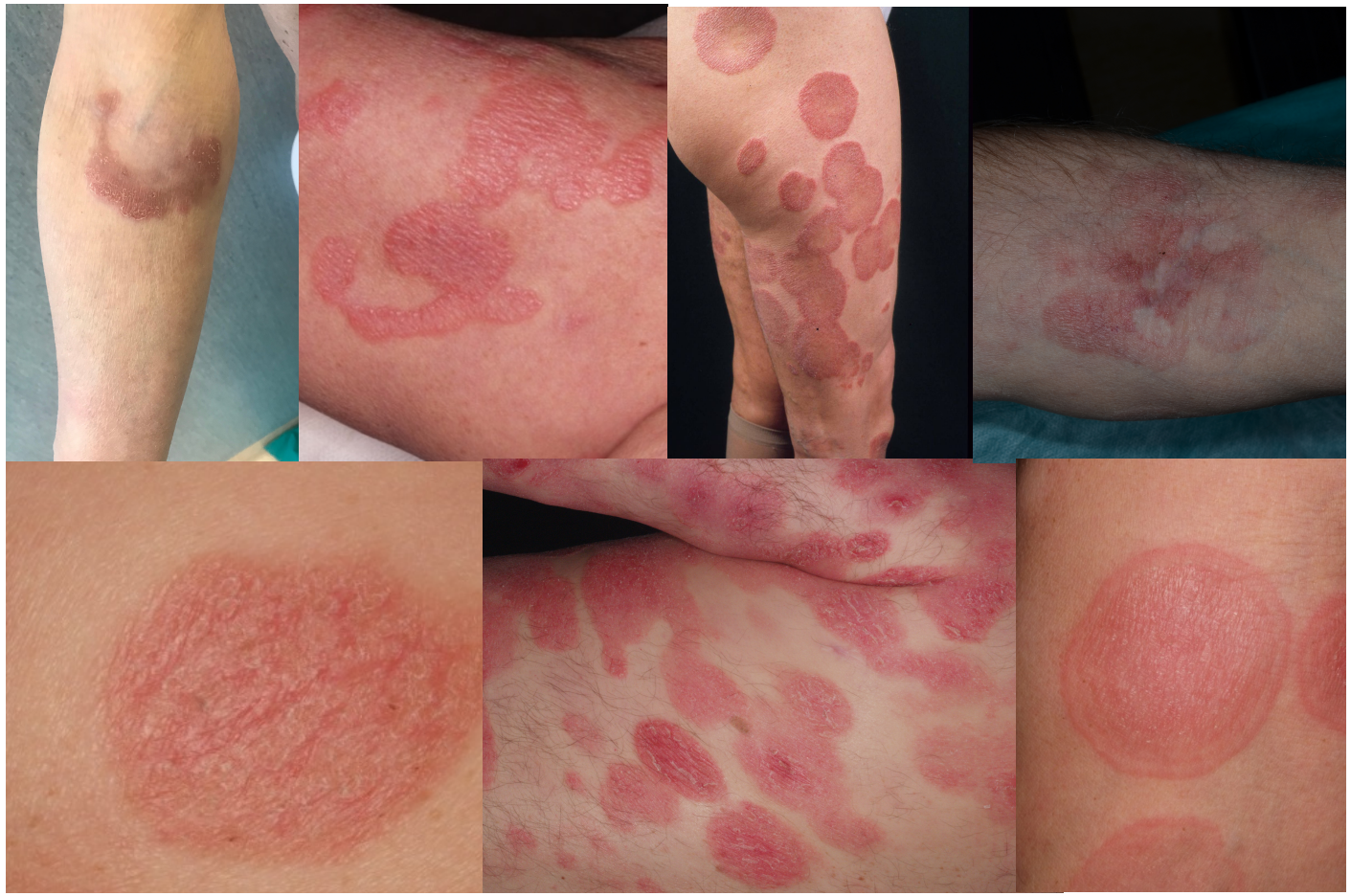
Original Article

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

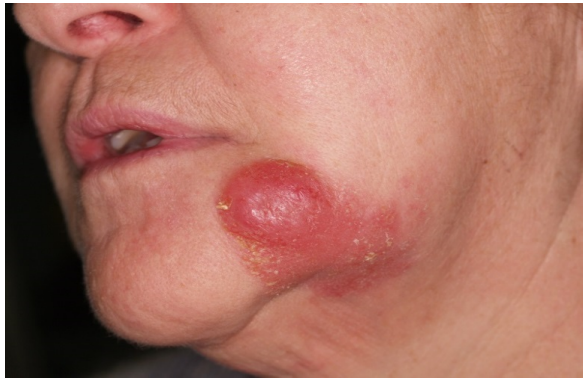
Pedro Horna,[1] Lynn C. Moscinski,[2] Lubomir Sokol,[3] and Haipeng Shao[2]*

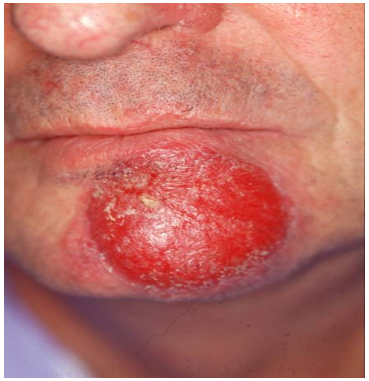


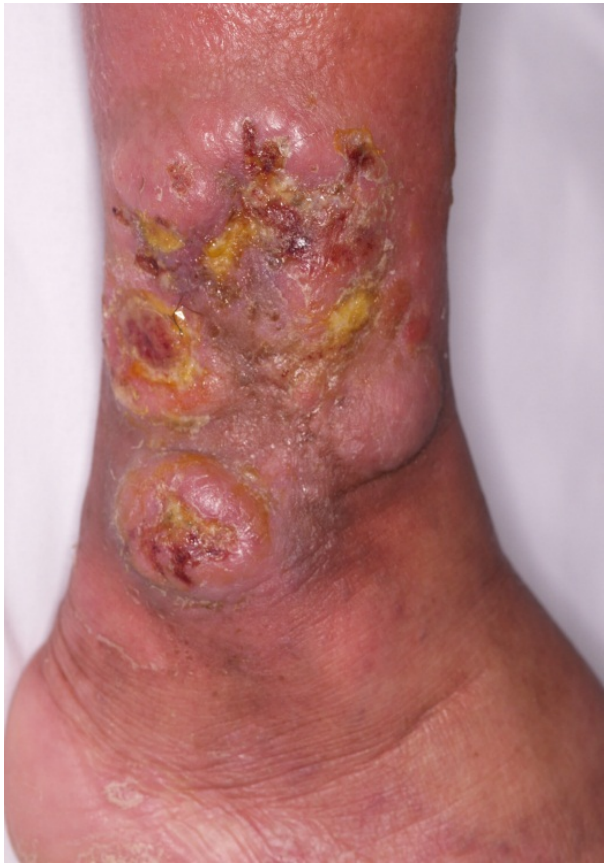
MF - PLAQUE

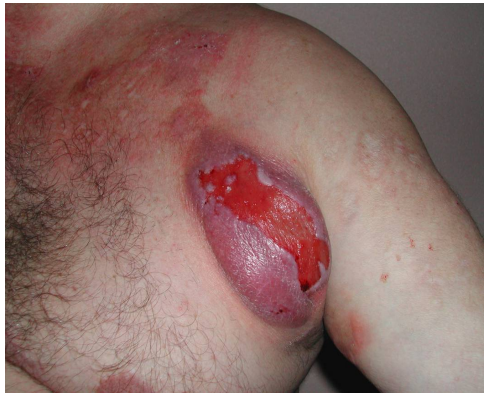


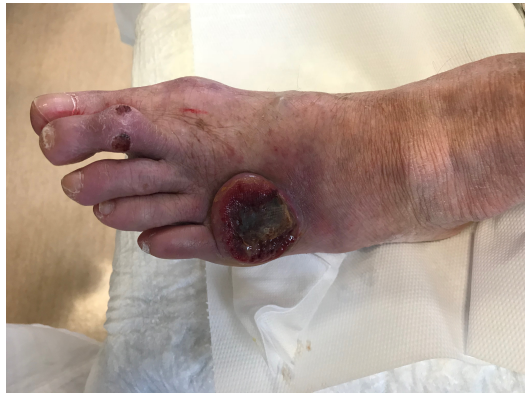
MF - TUMOR



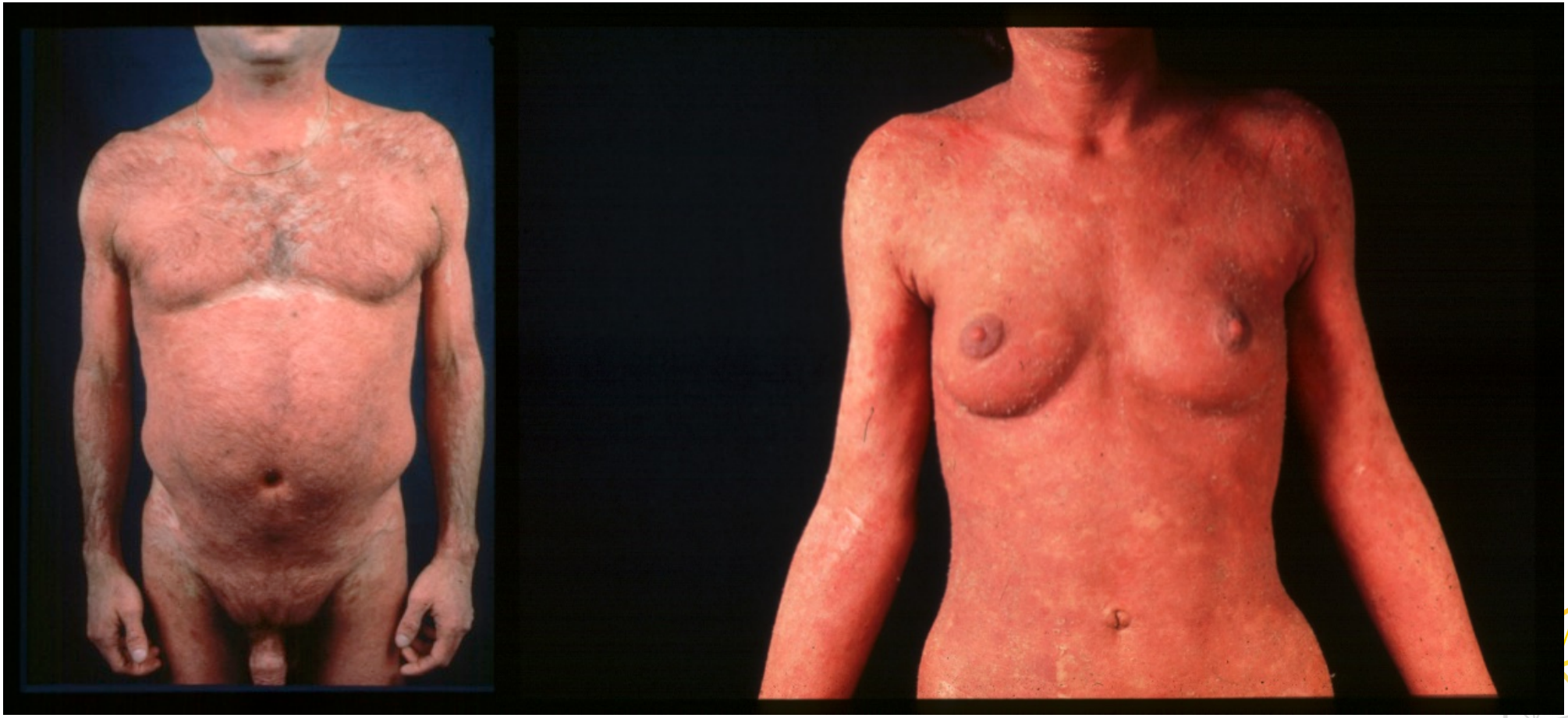




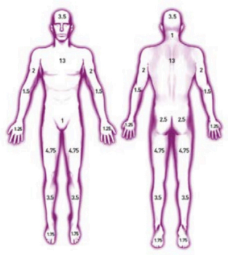




MF - ERYTHRODERMA



MODIFIED SEVERITY WEIGHTED ASSESSMENT TOOL (MSWAT)



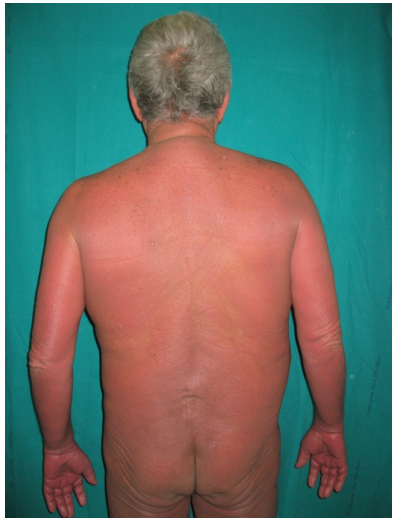
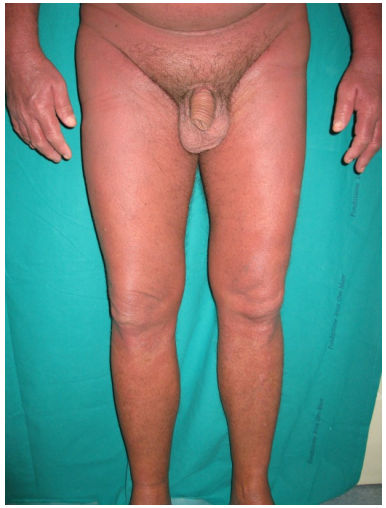
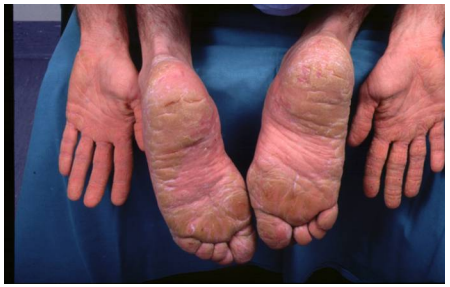
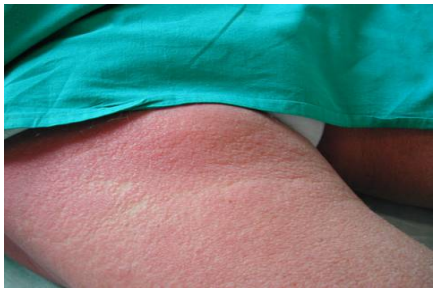
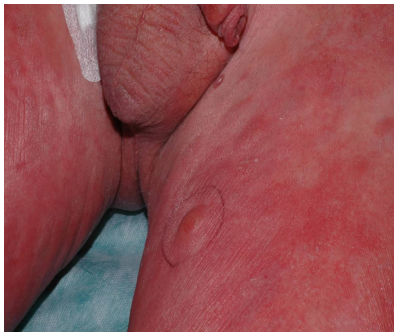
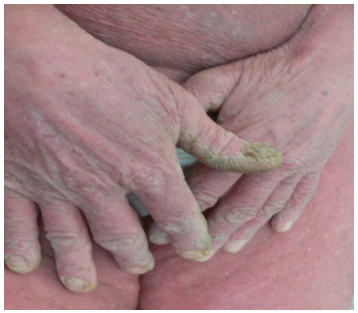
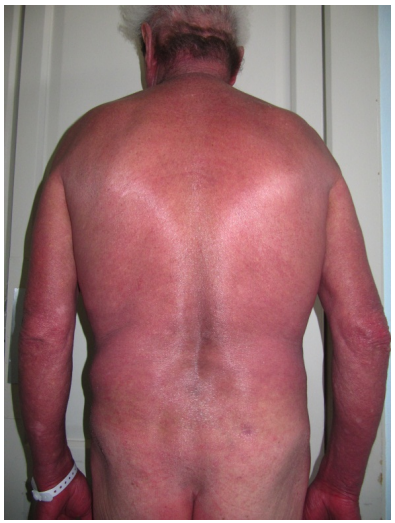
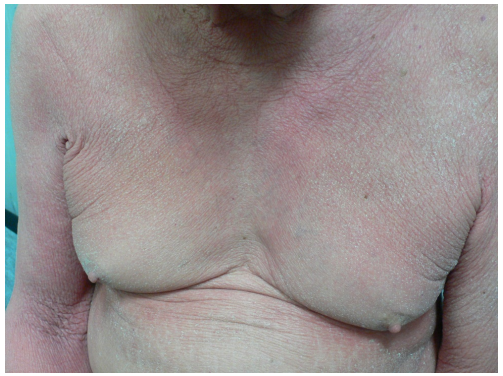
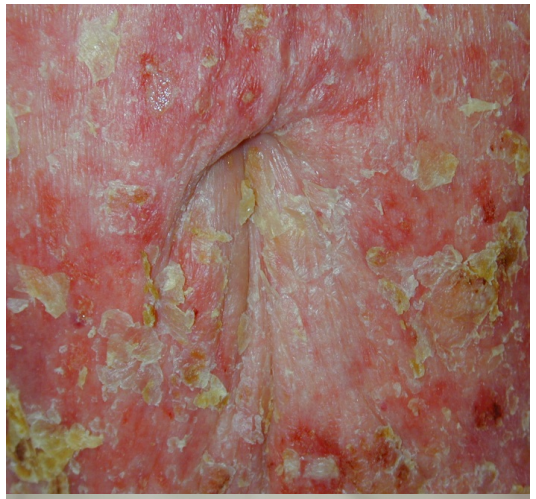
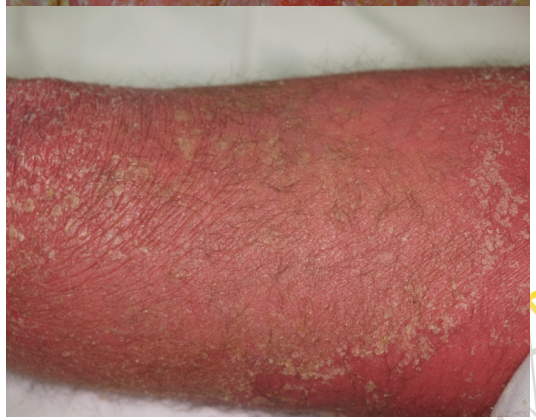
- The body is divided into 12 regions with pre-assigned percentages of total body surface area (BSA).
- The extent of skin disease is assessed for each region and weighted for more severe lesion per the assessment table below.
- The patient's palm (including four fingers and thumb), measured from wrist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

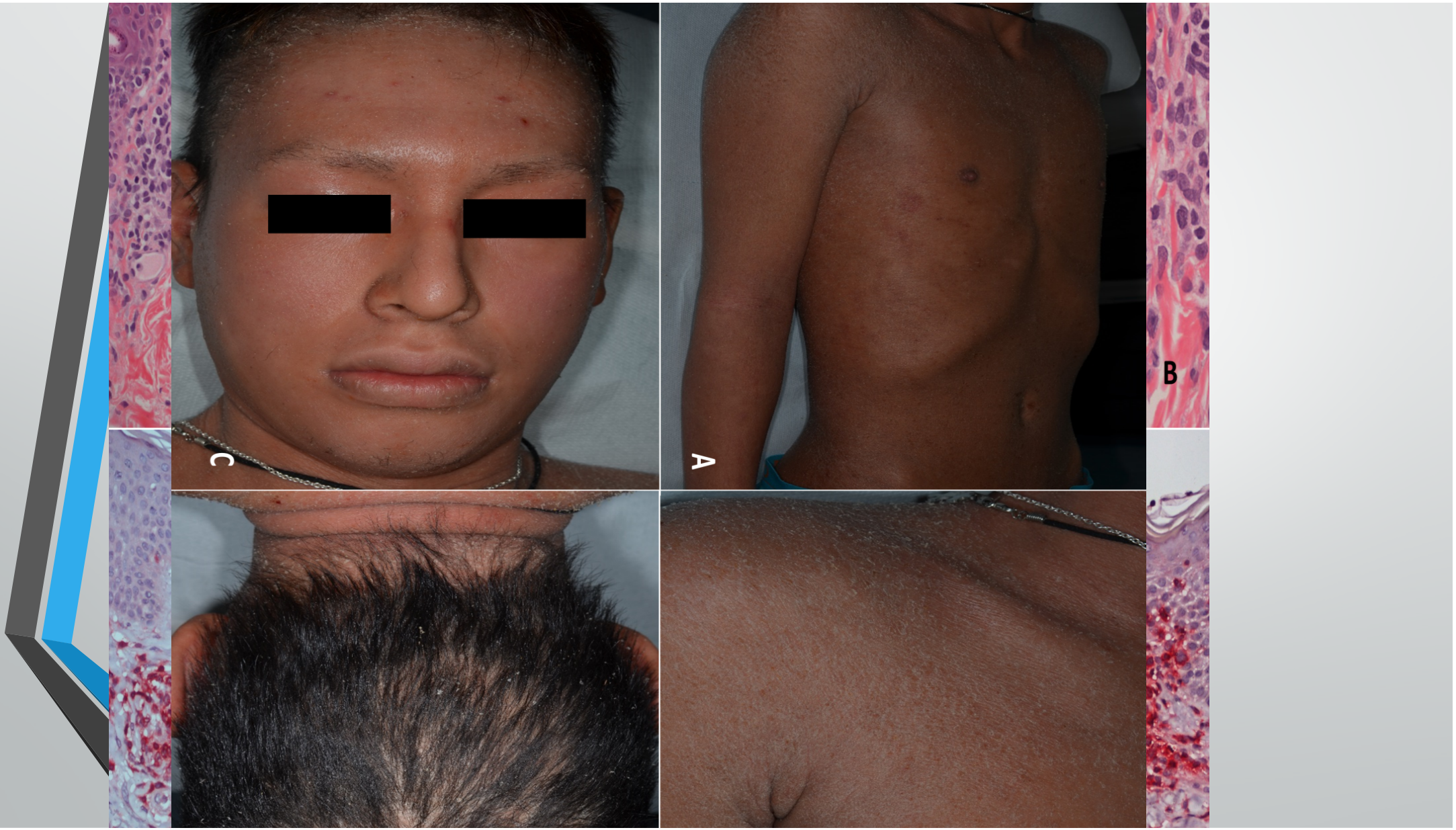
		Assessment of involvement in patient's skin		
Body region	**% BSA in Body region**	**Patch[a]**	**Plaque[b]**	**Tumour[c]**
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA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

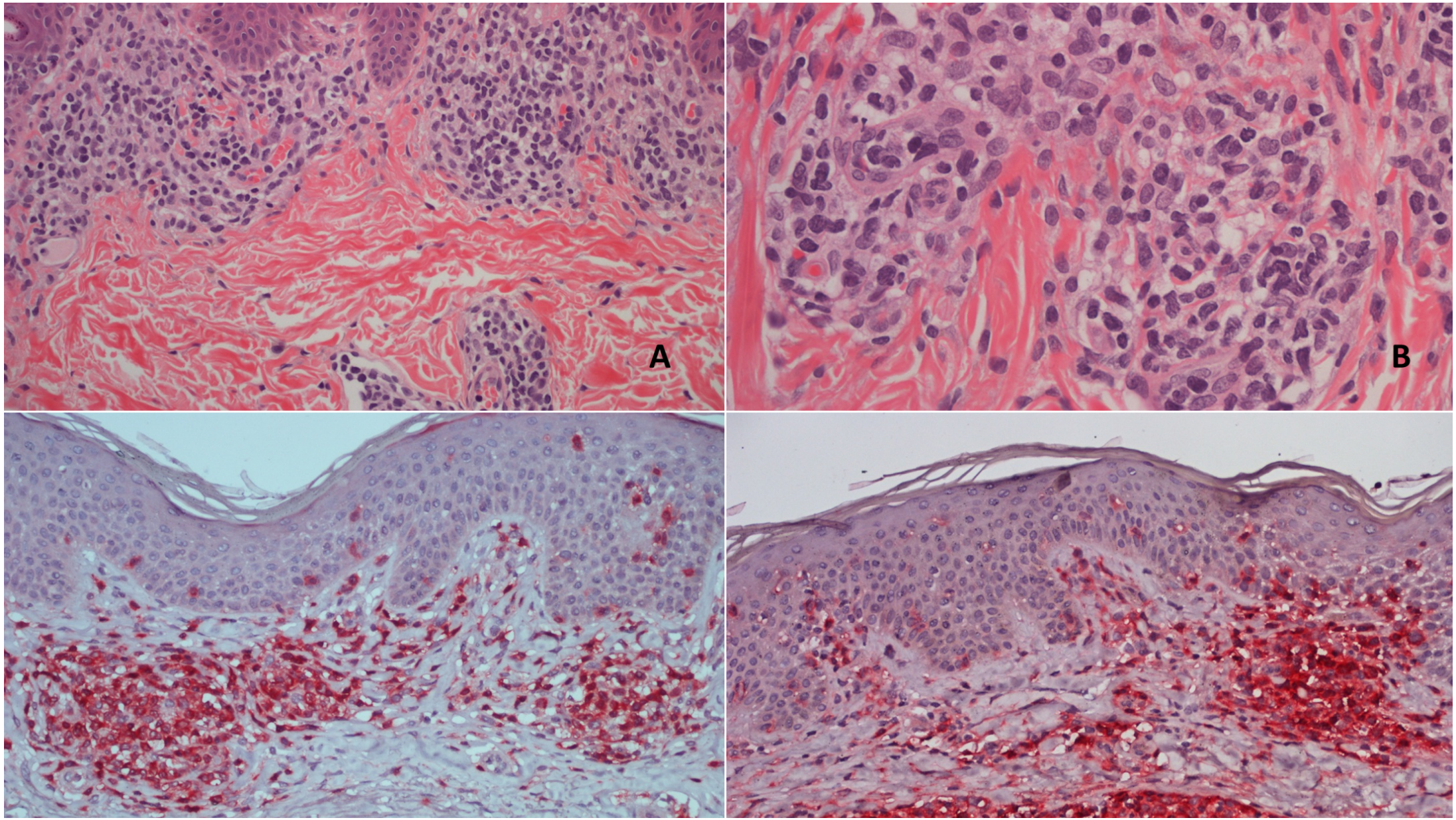
SÉZARY SYNDROME

- 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

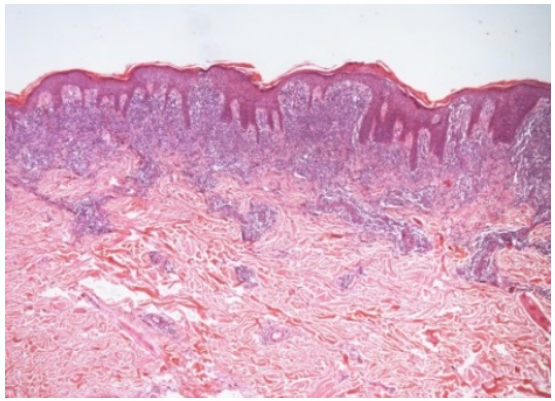











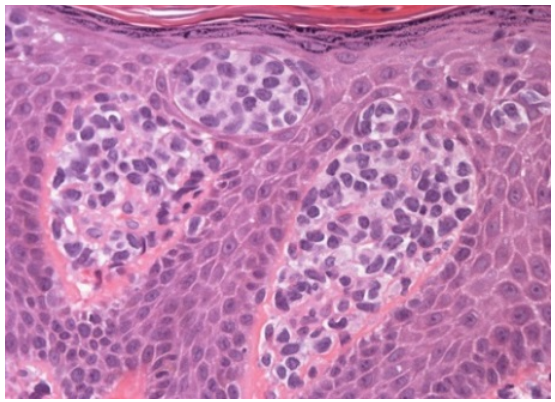

A
B
C

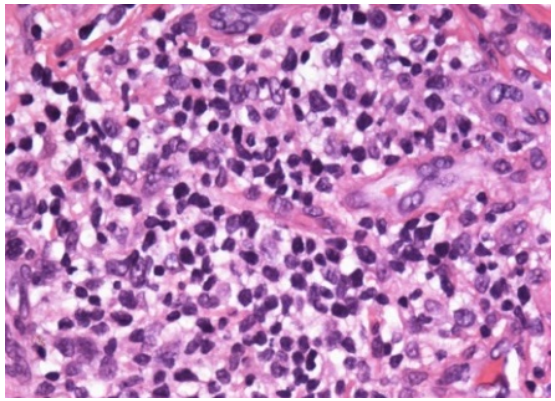

A
B

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



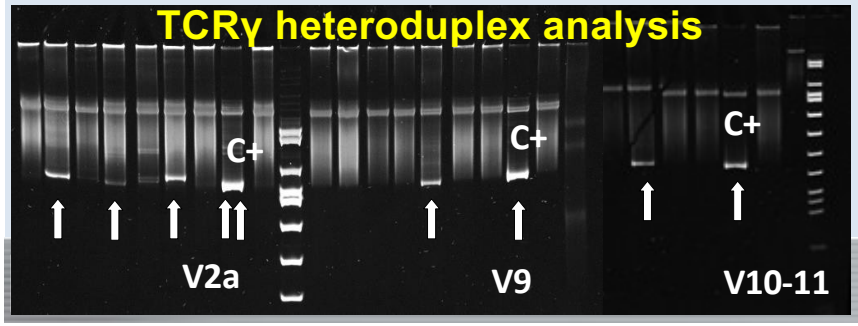


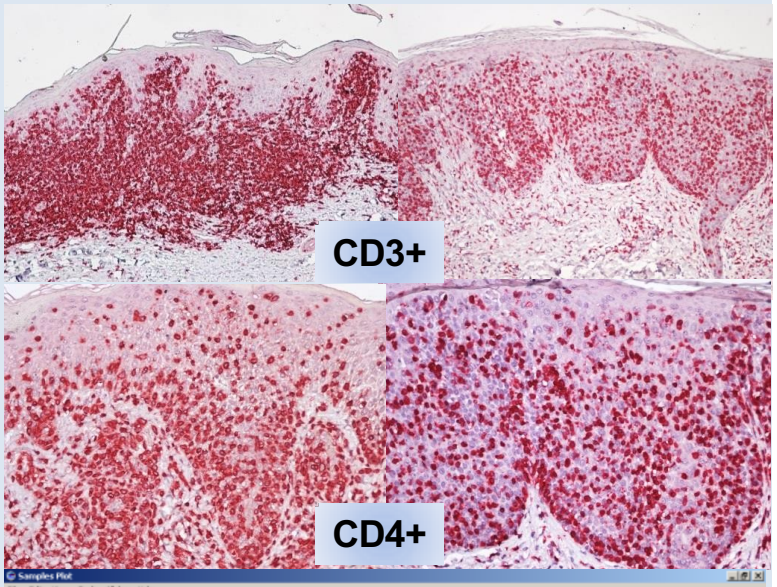


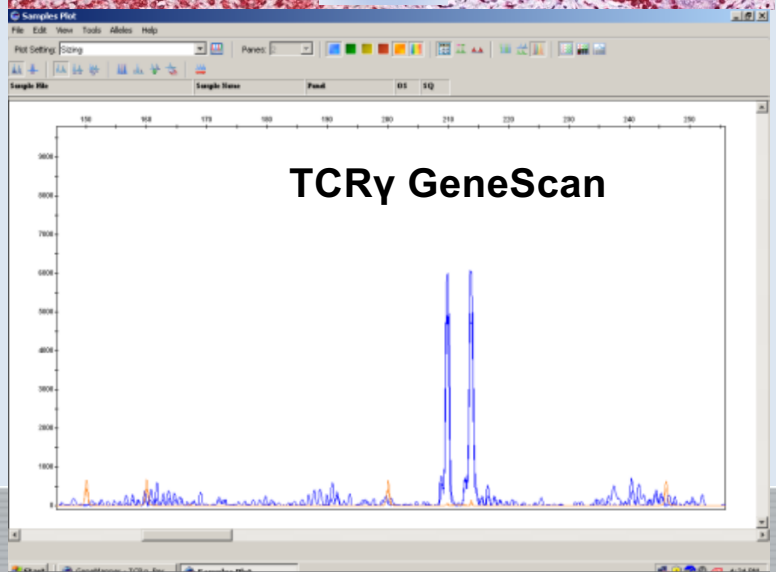
MF: Immunophenotype/molecular data

Phenotype: tumour T-cell express a βF1+, CD3+, CD4+, CD29+, CD45RO+, CLA+, CCR4+, CXCR4+ phenotype and are CD7, CD8, CCR7/L-selectin, CD27 negative (***effector memory T-cell***). Less frequently MF cells may express a cytotoxic phenotype: CD8+ and/or CD56+ /Tia-1+.

Molecular studies to detect monoclonal T-cell population in the skin and extracutaneous localizations must be done by using PCR and specific primers (i.e. BIOMED-1/2) for the TCRγ or β or δ (heteroduplex analysis or GeneScan). Microarrays CGH showed in MF gains of 1p25-31, 7p22-11.2, 7q21,7q13, 17q and losses of 9p21, 10p11.2, 10q26 **(Lahranne et al J. Invest. Dermatol. 2010; 130, 1707-18).**

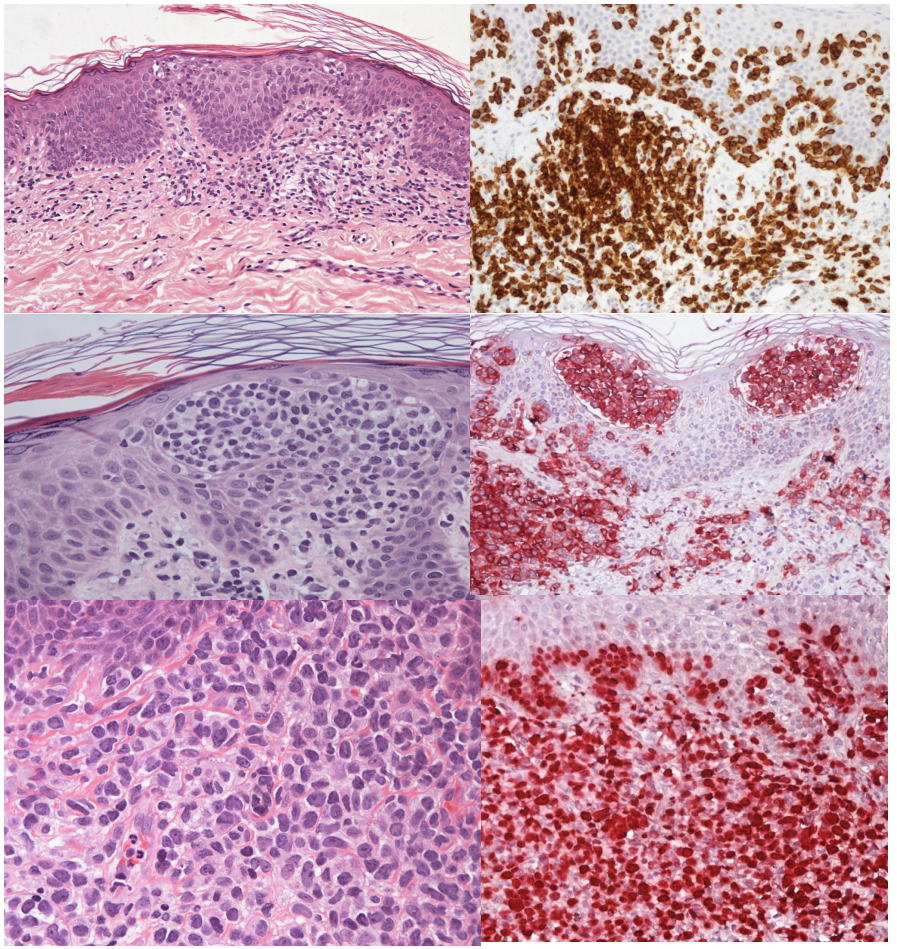




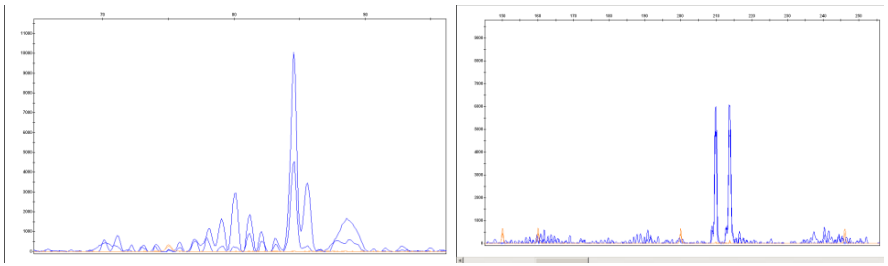


Neoplastic T-cells are

- **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)

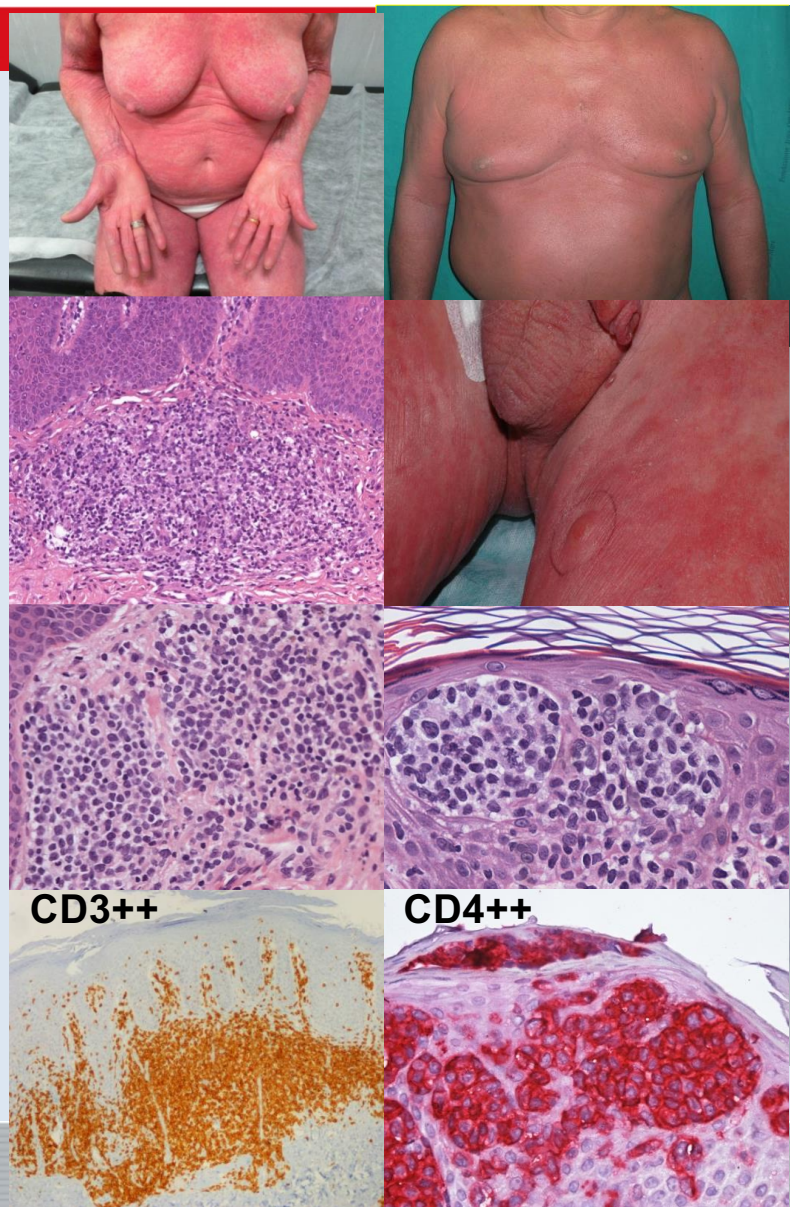


Molecular analysis by using PCR shows monoclonal rearrangement of the TCR



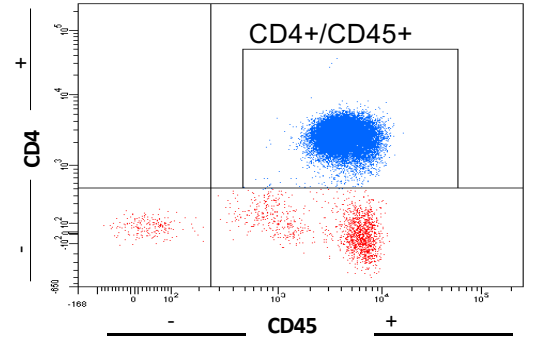
Sézary Syndrome (aggressive)

- 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.



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.



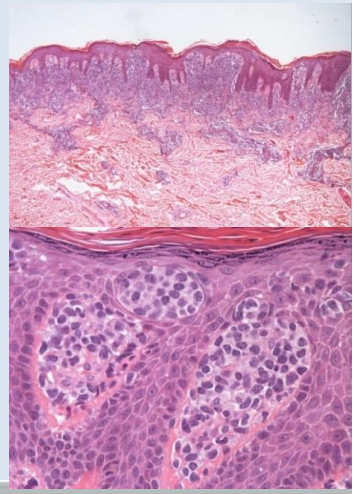
Sézary Syndrome – diagnostic criteria

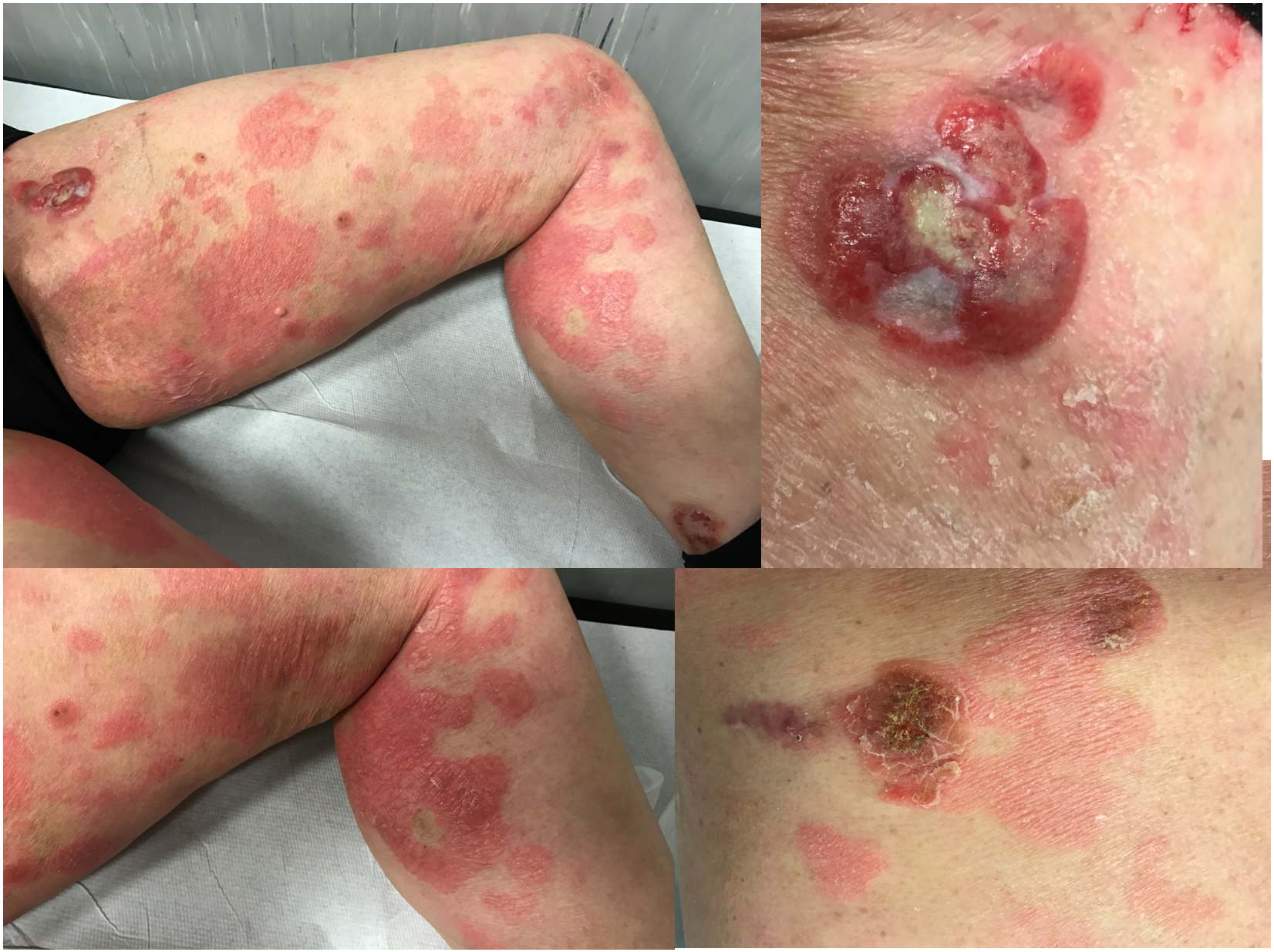
- ☐ Histopathologic features: MF-like (erythroderma stage III); skin biopsies sometimes may be devoid of specific diagnostic features; however in most cases medium and large cerebriform cells can be detected in the superficial dermis (dense perivascular pattern) and in the epidermis (Pautrier microabscesses).
- ☐ Immunoprofile: CD2+, CD3+, CD4+, CD5+, CD7-/+, CD26-, CD27+, CD45RO+, CCR4+, CD30-, CCR7+, L-selectin+ (***central memory T cells***), PD1+, CD30+/- (>33% of cells) ; rare cases may be CD3-, CD4-/CD8- or CD8+ and CD45RA+.
- ☐ Detection of peripheral blood T-cell population (> 1000mm^3), with the above mentioned immunoprofile. Sézary cells in peripheral blood > 20% ,

a. Expanded CD4+ T-cell population resulting in a CD4/CD8 ratio of more > 10 (not in early stage.)

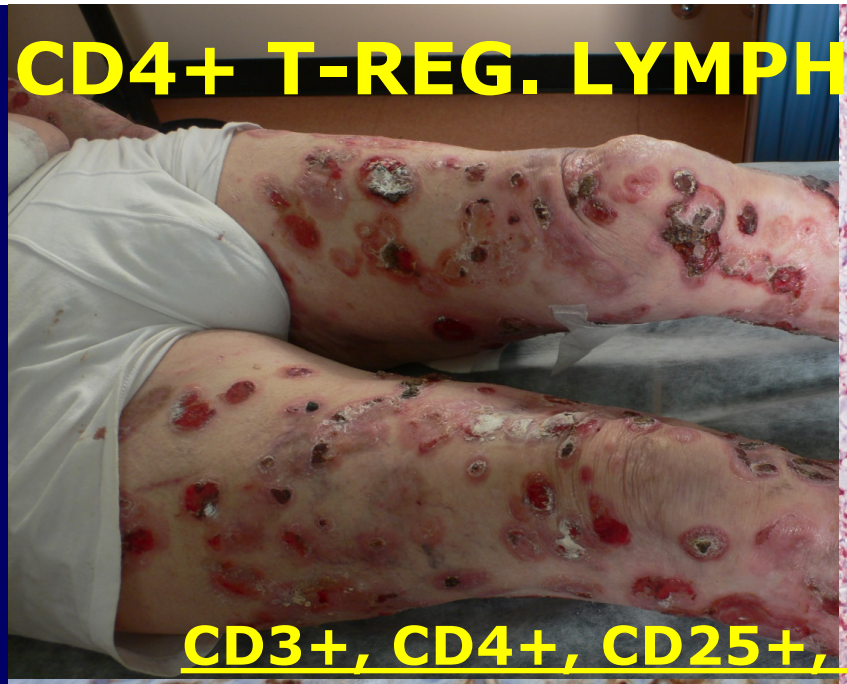
b. Loss of one or more pan T-cell markers

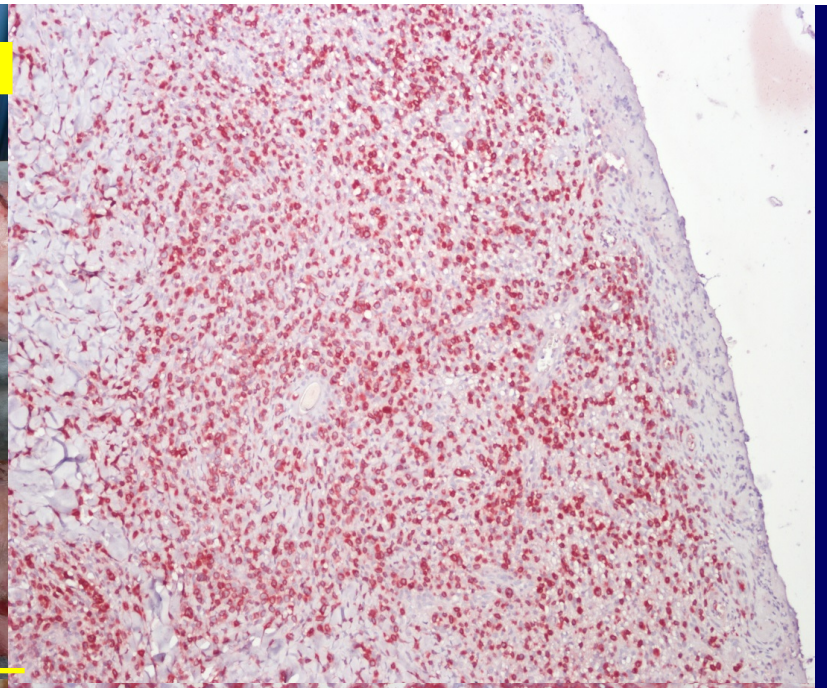
c. Detection of the same T-cell clone (by TCR-β analysis) in the skin, blood and lymph-nodes and of the cytogenetic SS profile (arrays-CGH): gains of 8q23-24.3, 17q23-24 and losses of 9p21, 10p12-11.2,, 10q22-24, 10q25-26, 17p13-q11. **(Lahranne et al J. Invest. Dermatol. (2010) 130, 1707-18)**.



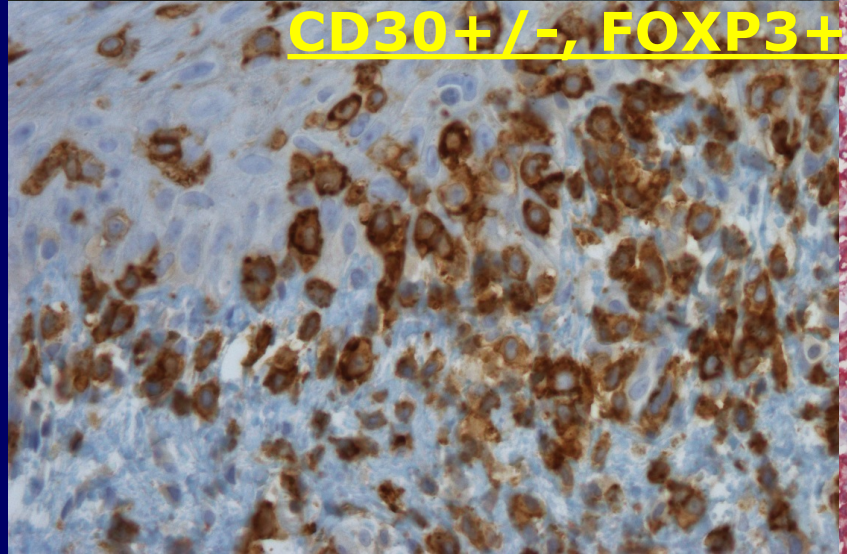


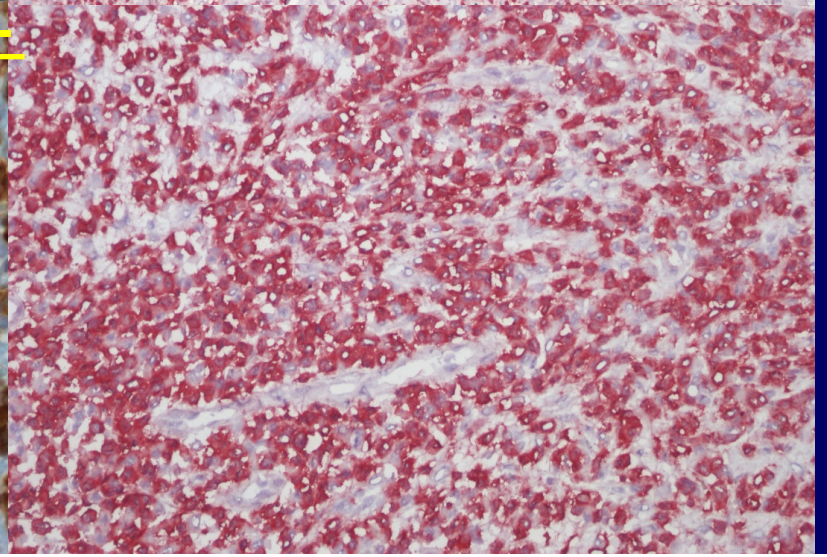
CD4+ T-REG. LYMPH





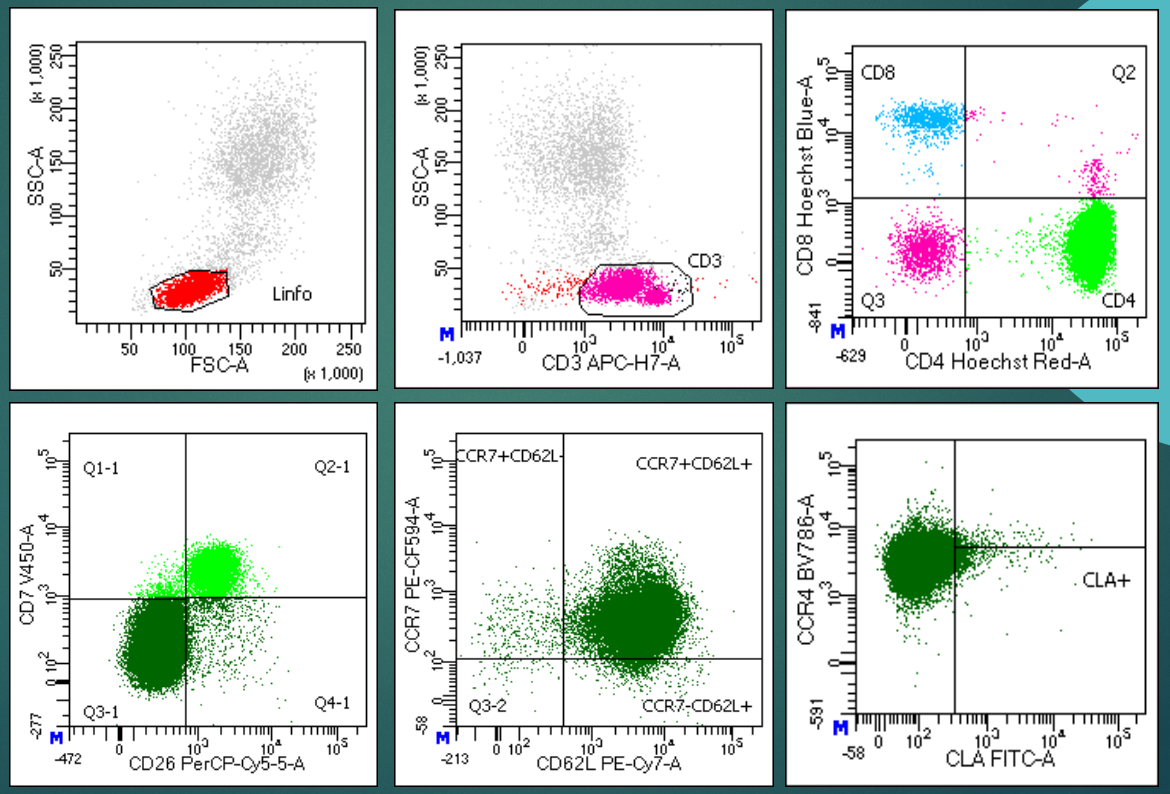
CD3+, CD4+, CD25+, CD30+/-, FOXP3+





1 Project – peripheral blood

12. aSS IVA1



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

- Rare, provisional entity

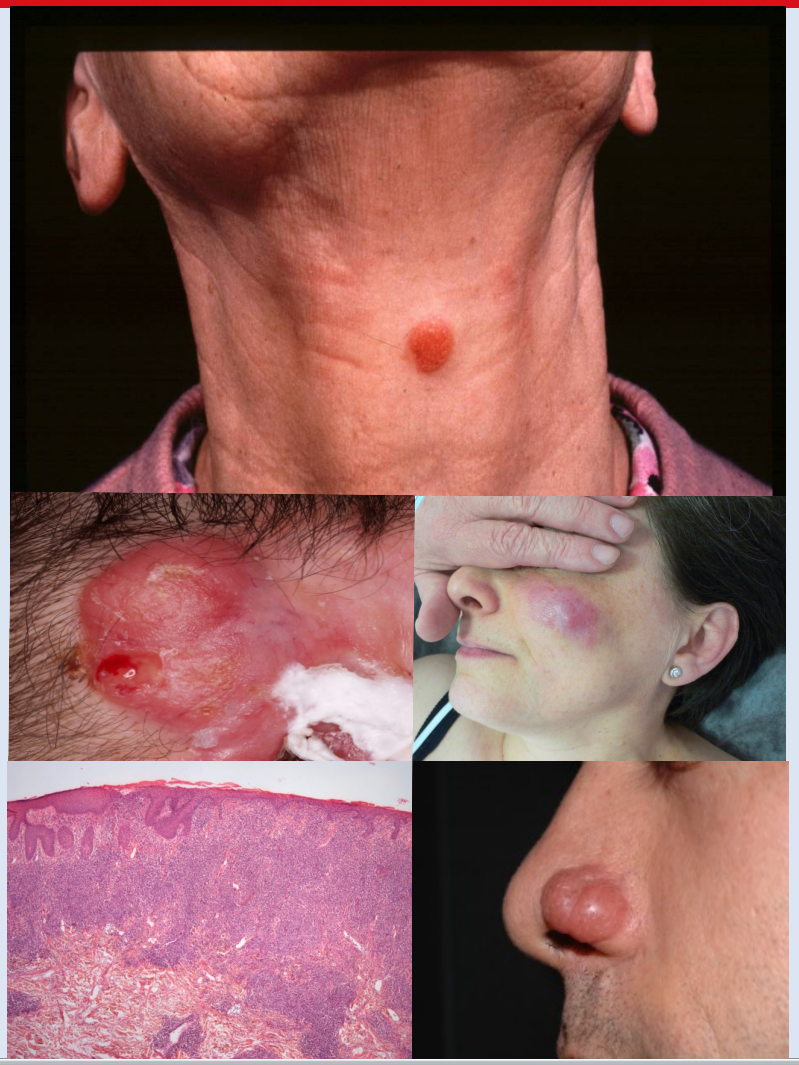
- Solitary nodule or plaque; more frequent on head and neck

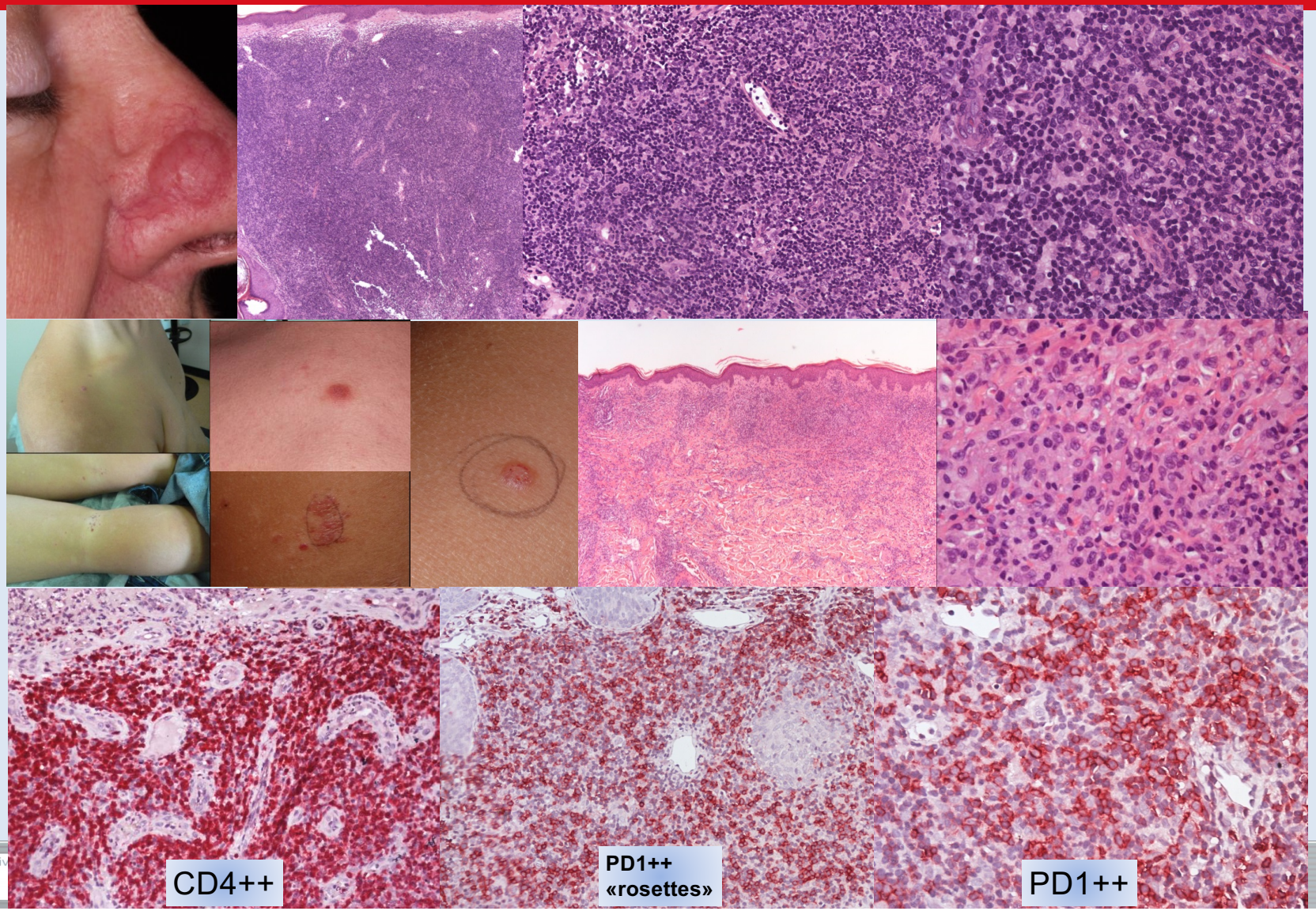
- No systemic symptoms

- Favourable outcome, OOS 5y 100%

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

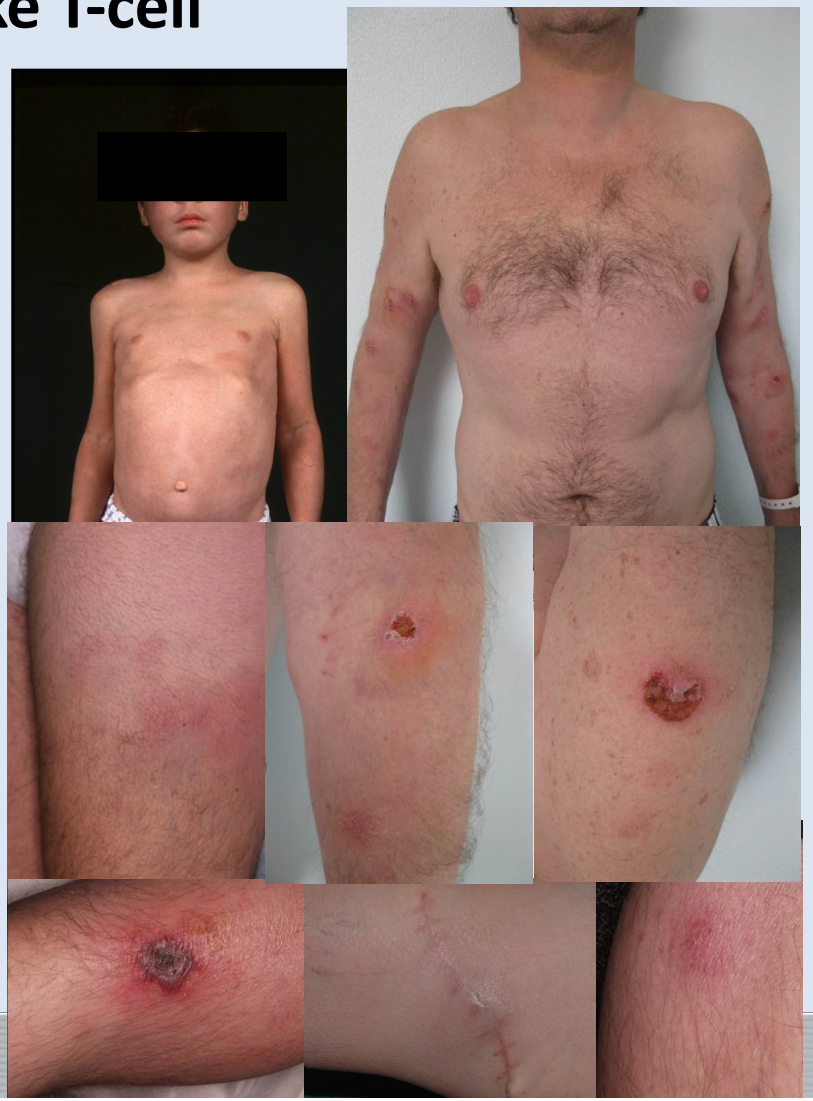
- Immunoprofile: CD3+, CD4+, CD8-, CD30-, EBV-, PD1+ (rosettes of + cells)




CD4++
PD1++
«rosettes»
PD1++

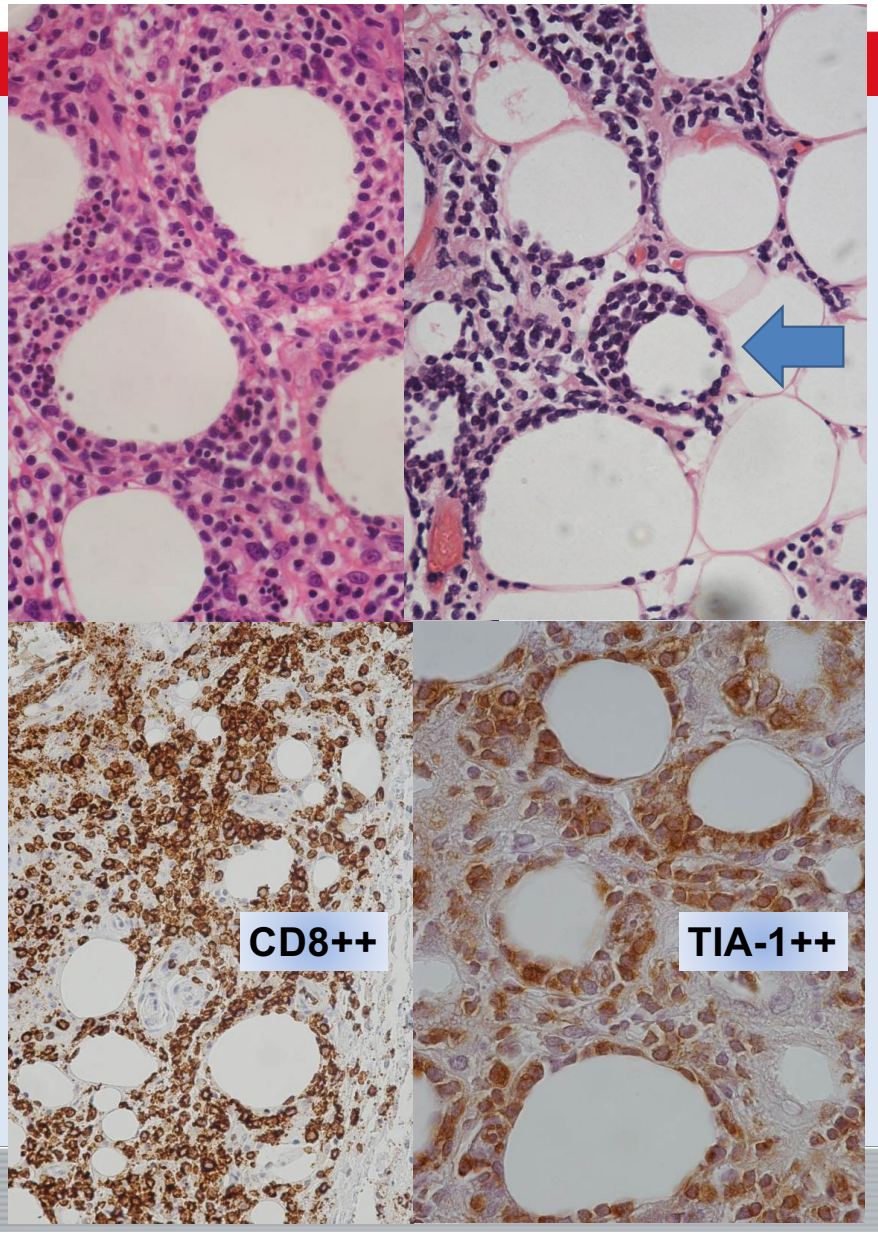
Subcutaneous panniculitis-like T-cell Lymphoma (Indolent)

- 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

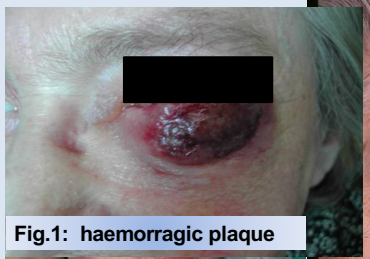


Fig.1: haemorragic plaque

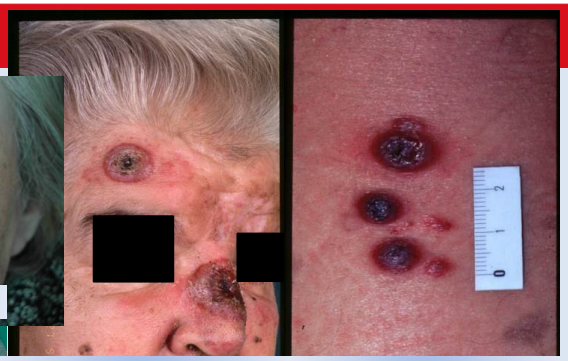


Fig.2: ulcerated verrucoid nodules

Fig.3: typical papulo-nodular necrotic lesions

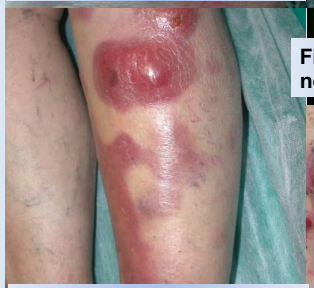


Fig.4: nodules-plaques, D.D. with large-B-cell lymphoma of the leg

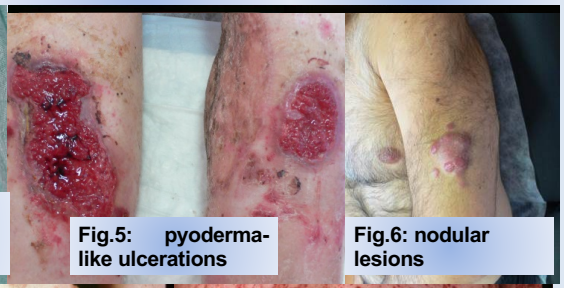


Fig.5: pyoderma-like ulcerations

Fig.6: nodular lesions

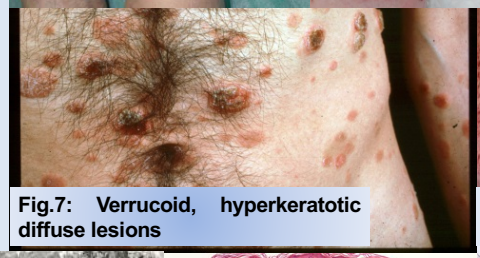


Fig.7: Verrucoid, hyperkeratotic diffuse lesions

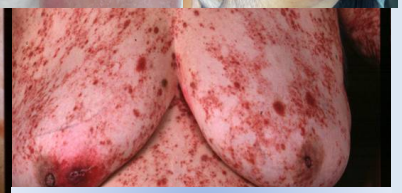
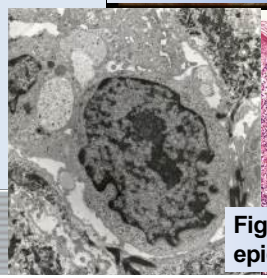


Fig.8: purpuric diffuse eruption (coagulopathy)



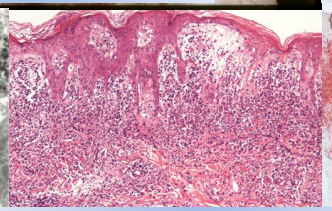


Fig.9: histology: note the highly epidermotropic-angiocentric infiltrate.

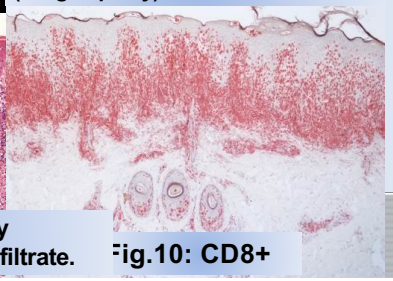
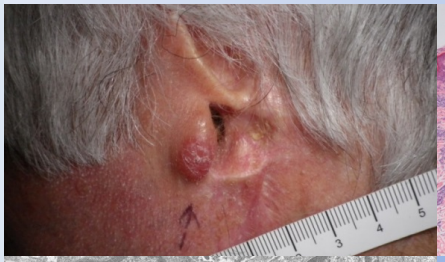
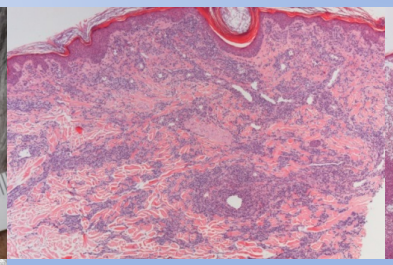


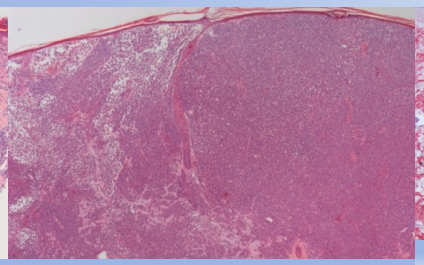
Fig.10: CD8+

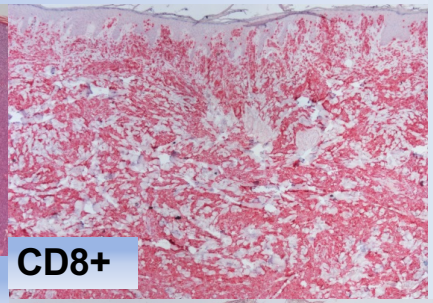
Primary cutaneous acral CD8+ T-cell lymphoma :

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





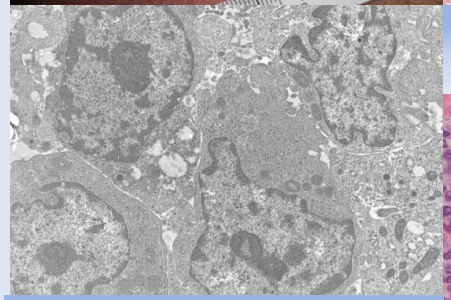




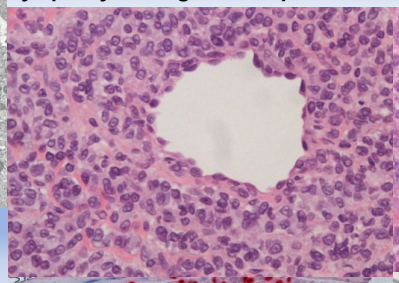
CD8+

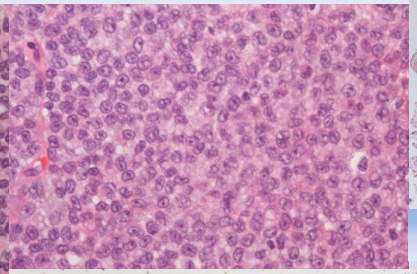
Early lesion: monotonous proliferation of small-medium size lymphocytes: angiocentric pattern

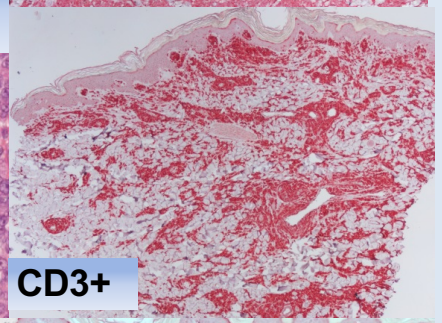
Nodule: proliferation of blasts-like cells with central nucleoli and abundant clear cytoplasm



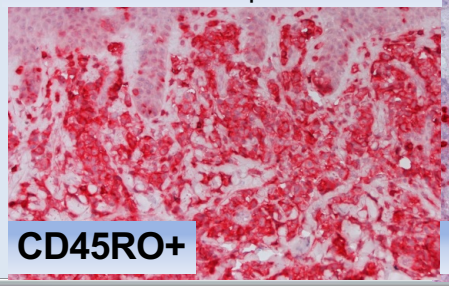
PTL of the Ear: Electron Microscopy showing lymphoid cells with roundish nuclei, abundant clear cytoplasm, cytotoxic granules, central nucleoli and villous plasma membrane



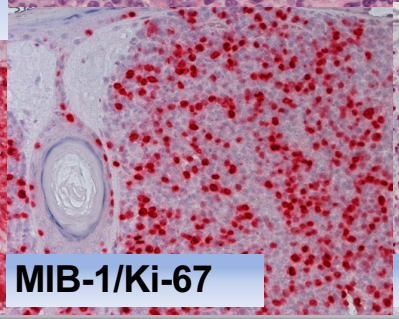




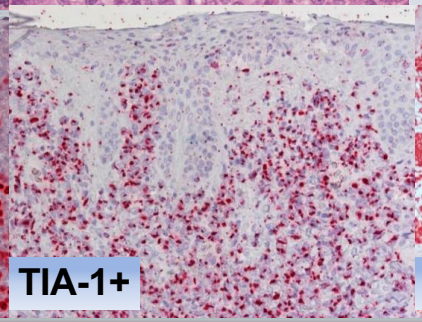
CD3+



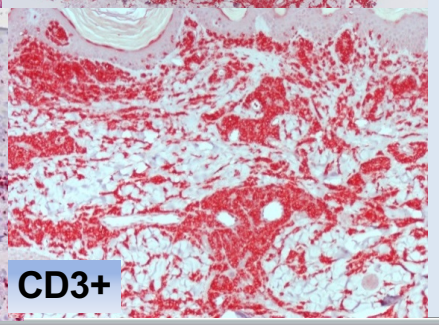
CD45RO+



MIB-1/Ki-67



TIA-1+

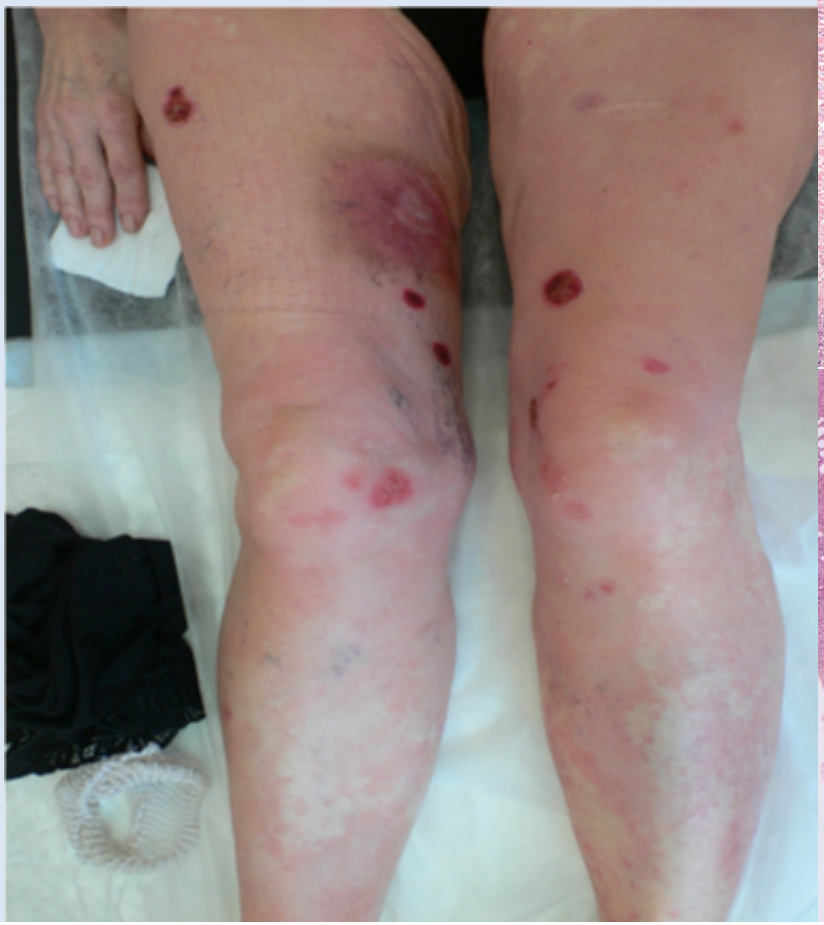


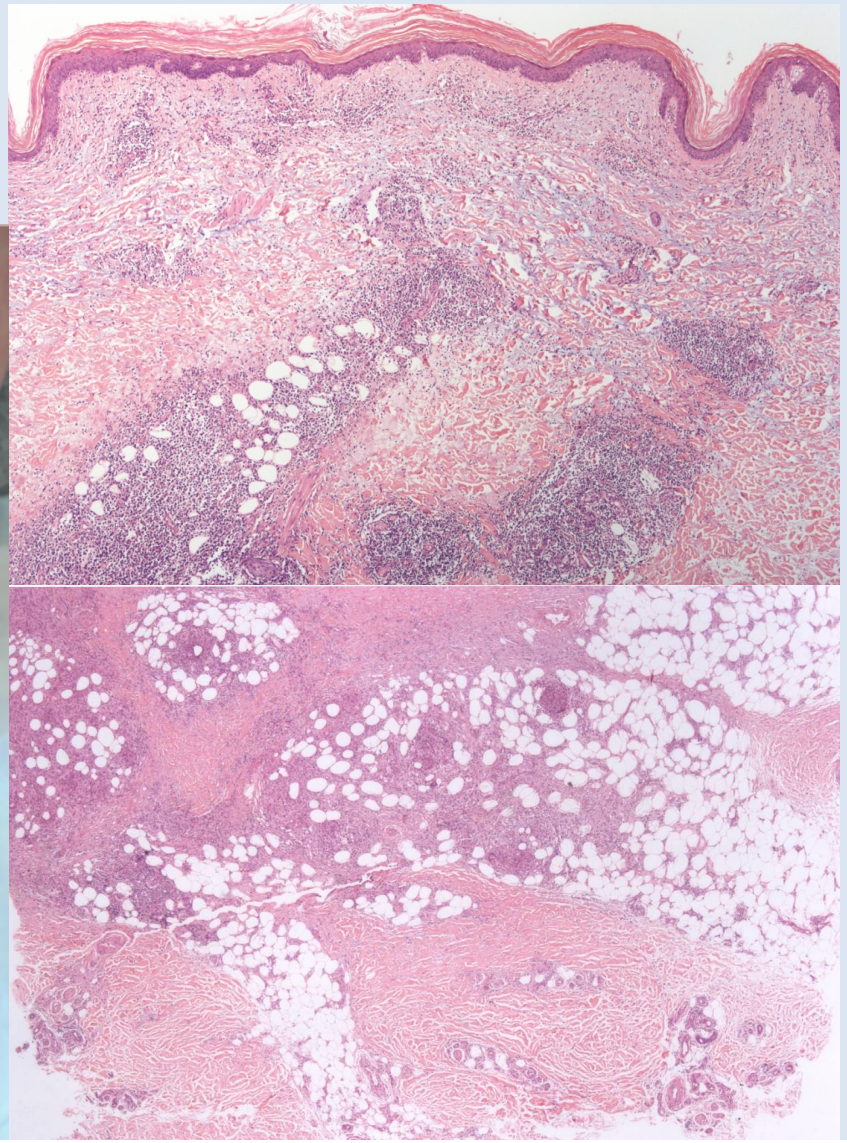
CD3+

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+

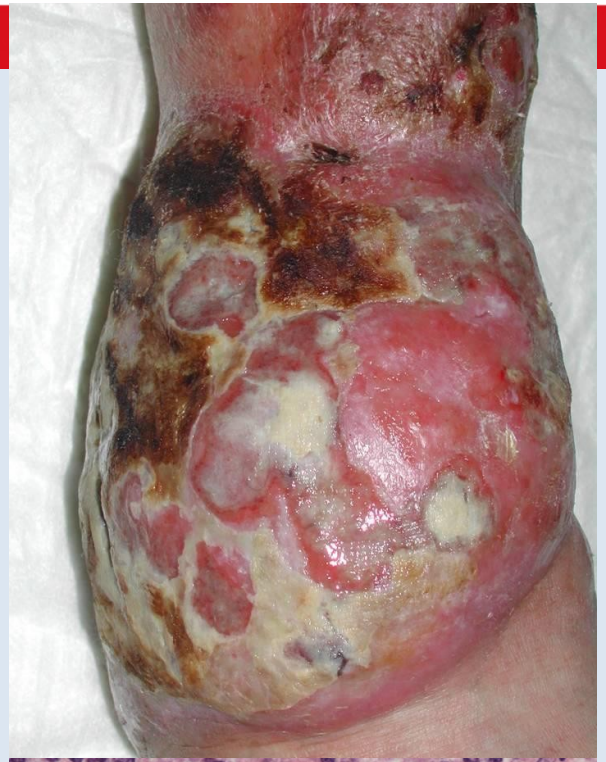
C-GD-TL with SPTCL presentation: the epidermis and dermis are also infiltrated by neoplastic cells.

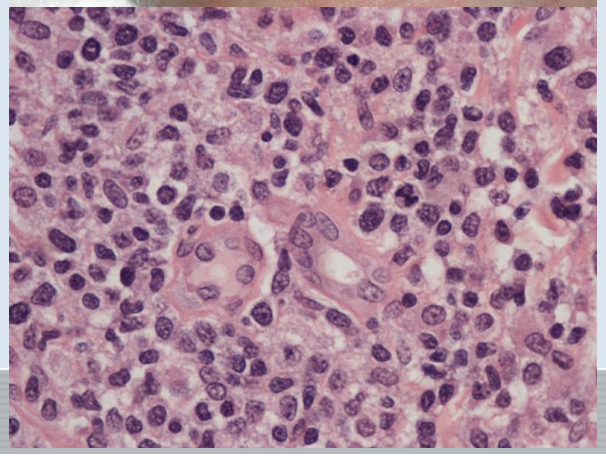




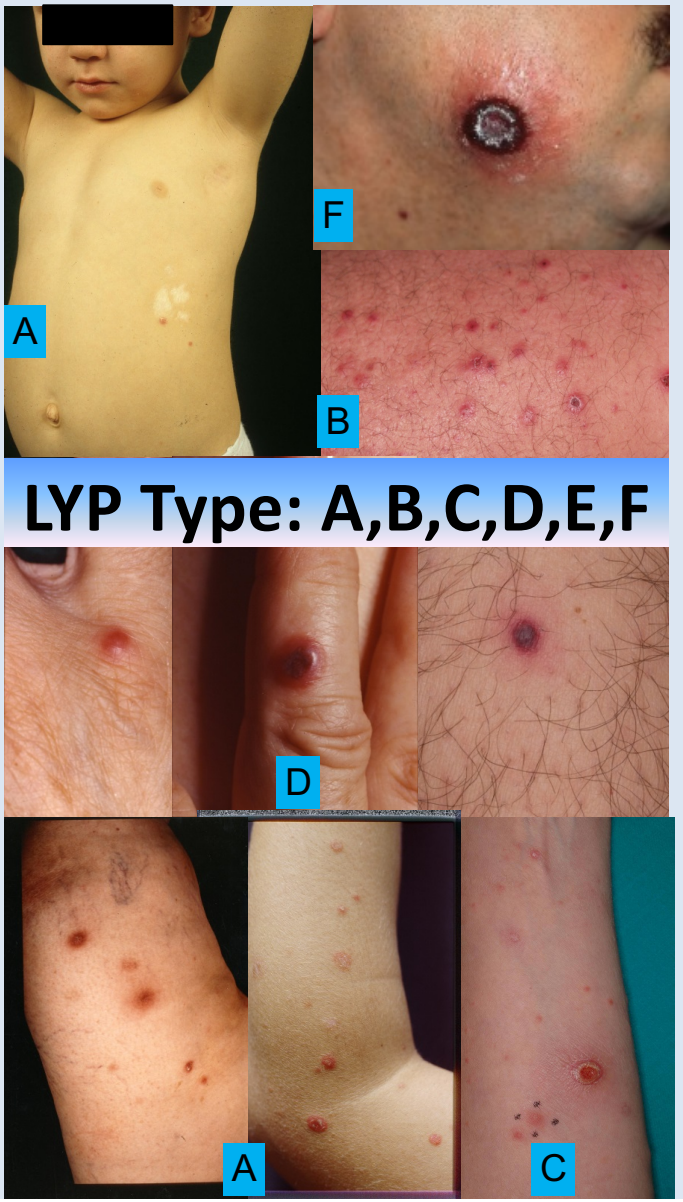
EXTRANODAL PC ENT-NK/T LYMPHOMA (aggressive)

- 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



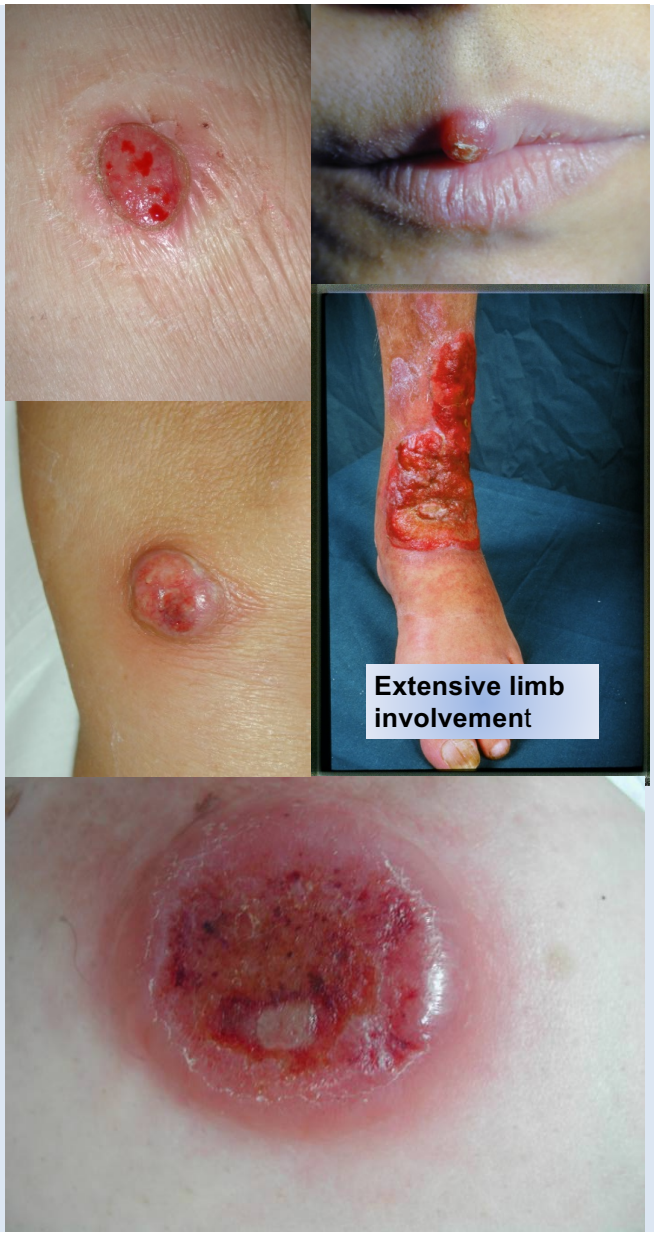


- Eruption of self-healing papular or papulo-nodular elements (few to many) sometimes covered by necrotic crust.
- Disease can be chronic and progress towards other forms of cutaneous (MF, PC-ALCL) or nodal lymphoma (ALCL and Hodgkin's disease).
- Incidence of progression to lymphoma is variable (4% and 10%).
- According to specific histopathologic features some subtypes are recognized.

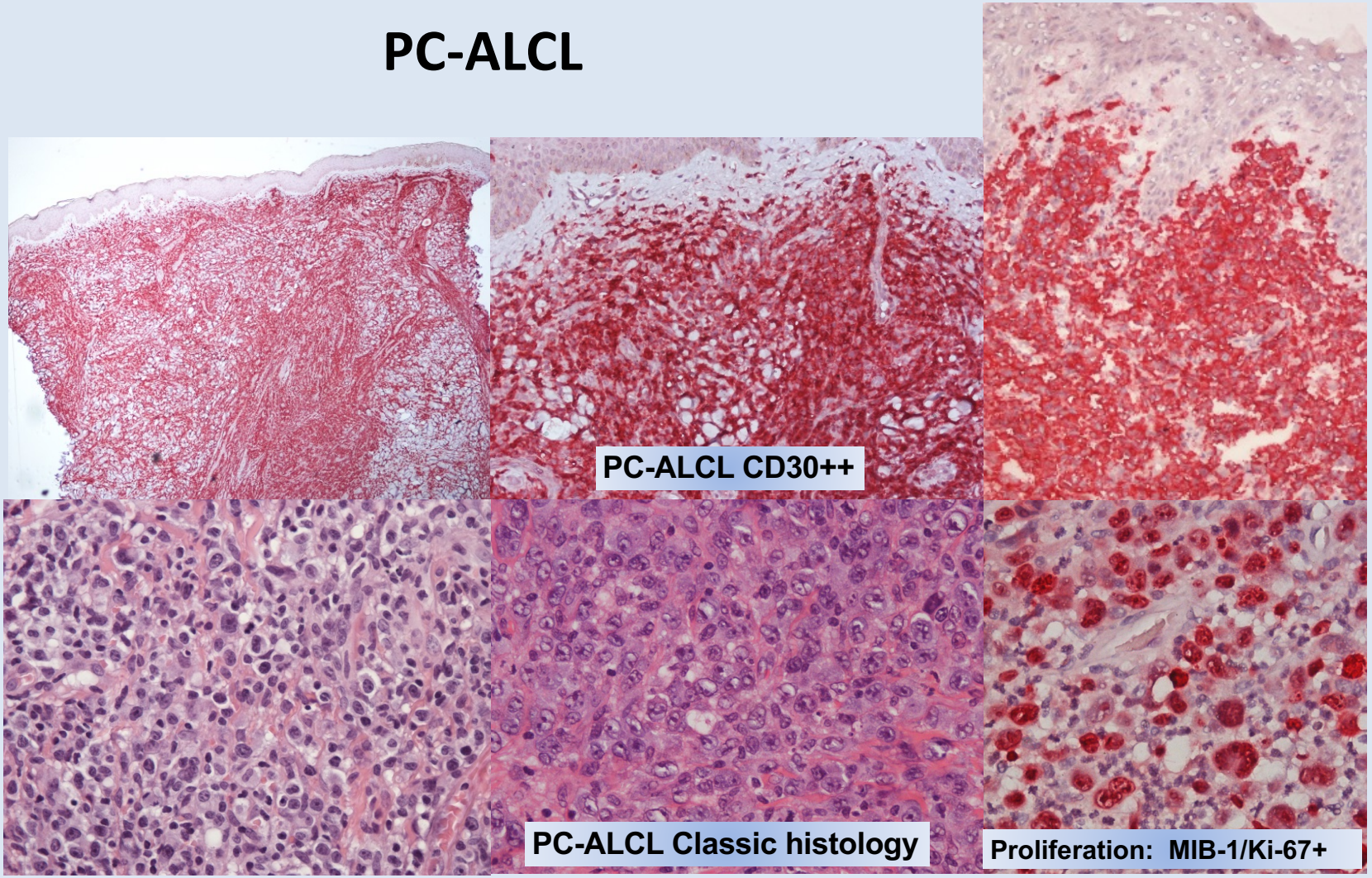


Primary cutaneous CD30 positive large cell lymphoma (PC-ALCL) (INDOLENT)

- 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%.



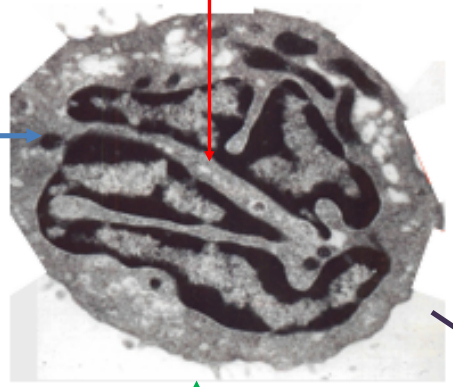
PC-ALCL

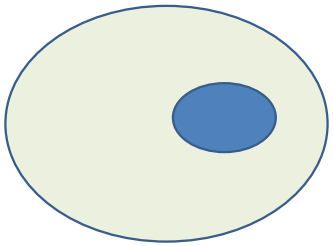

PC-ALCL CD30++
PC-ALCL Classic histology
Proliferation: MIB-1/Ki-67+

TERAPIA “TARGET” CTCL

NUCLEO
HDAC inhibitors
PNP: forodesine
DNA alkylating: mechlorethamine

PATHWAYS
JAK-STAT inhibitors





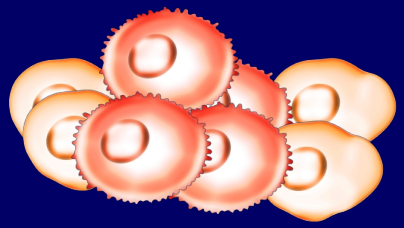
CHECK-POINT INHIBITORS
Anti-PD-1/PDL-1

STEM CELLS
Allo-HSCT

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

Targeting T-cell Lymphoma

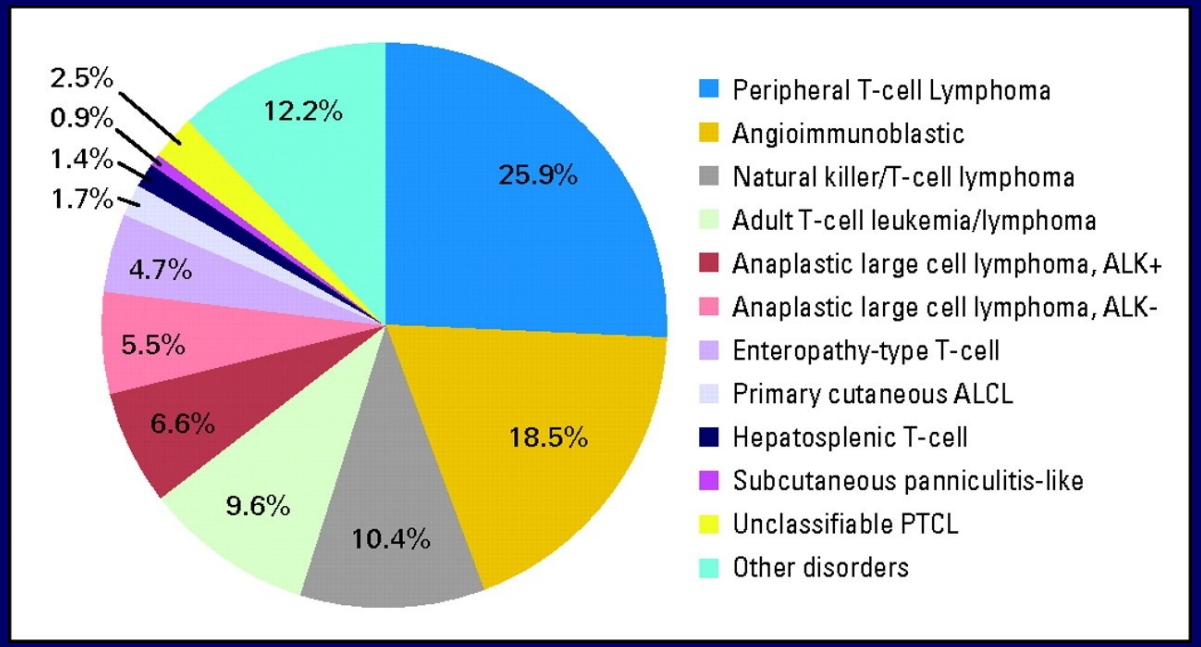
Surface Antigens/Receptors
CD2
CD4
CD25
CD30
Chemokine recepto



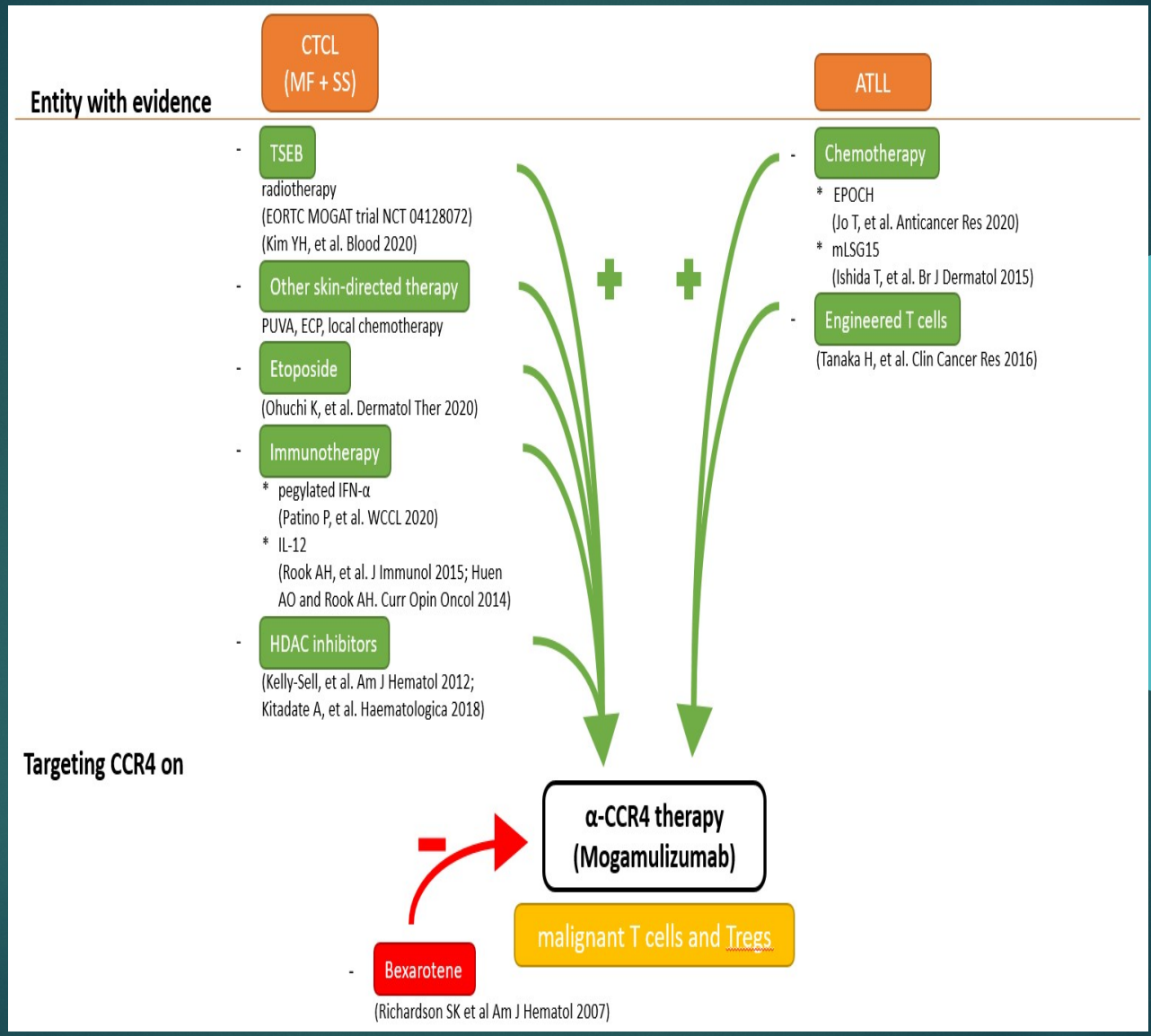
Microenvironmental Factors
Angiogenesis
Immunomodulation
Viral Pathogens

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

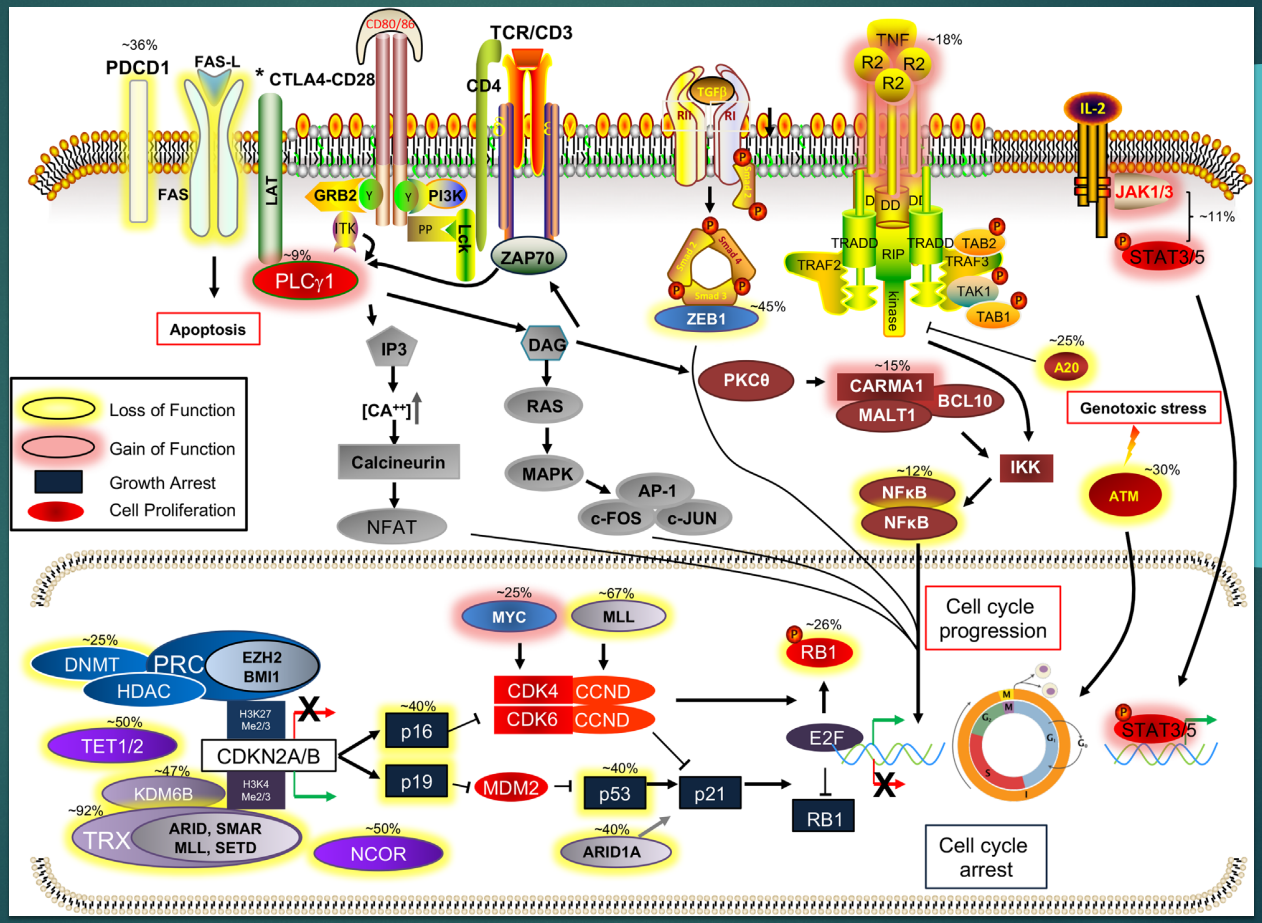
Fig 1. Distribution of 1,314 cases of PTCL by consensus diagnosis



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


Entity with evidence
CTCL (MF + SS)
ATLL
TSEB
radiotherapy
(EORTC MOGAT trial NCT 04128072)
(Kim YH, et al. Blood 2020)
Other skin-directed therapy
PUVA, ECP, local chemotherapy
Etoposide
(Ohuchi K, et al. Dermatol Ther 2020)
Immunotherapy
* pegylated IFN-α
(Patino P, et al. WCCL 2020)
* IL-12
(Rook AH, et al. J Immunol 2015; Huen AO and Rook AH. Curr Opin Oncol 2014)
HDAC inhibitors
(Kelly-Sell, et al. Am J Hematol 2012; Kitadate A, et al. Haematologica 2018)
Chemotherapy
* EPOCH
(Jo T, et al. Anticancer Res 2020)
* mLSG15
(Ishida T, et al. Br J Dermatol 2015)
Engineered T cells
(Tanaka H, et al. Clin Cancer Res 2016)
Targeting CCR4 on
α-CCR4 therapy (Mogamulizumab)
malignant T cells and Tregs
Bexarotene
(Richardson SK et al Am J Hematol 2007)

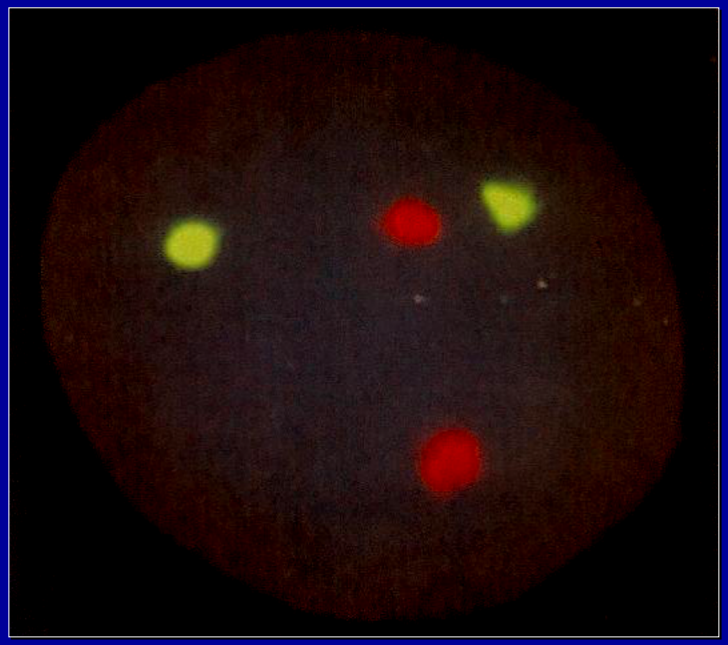
MF/SS – genomic landscape



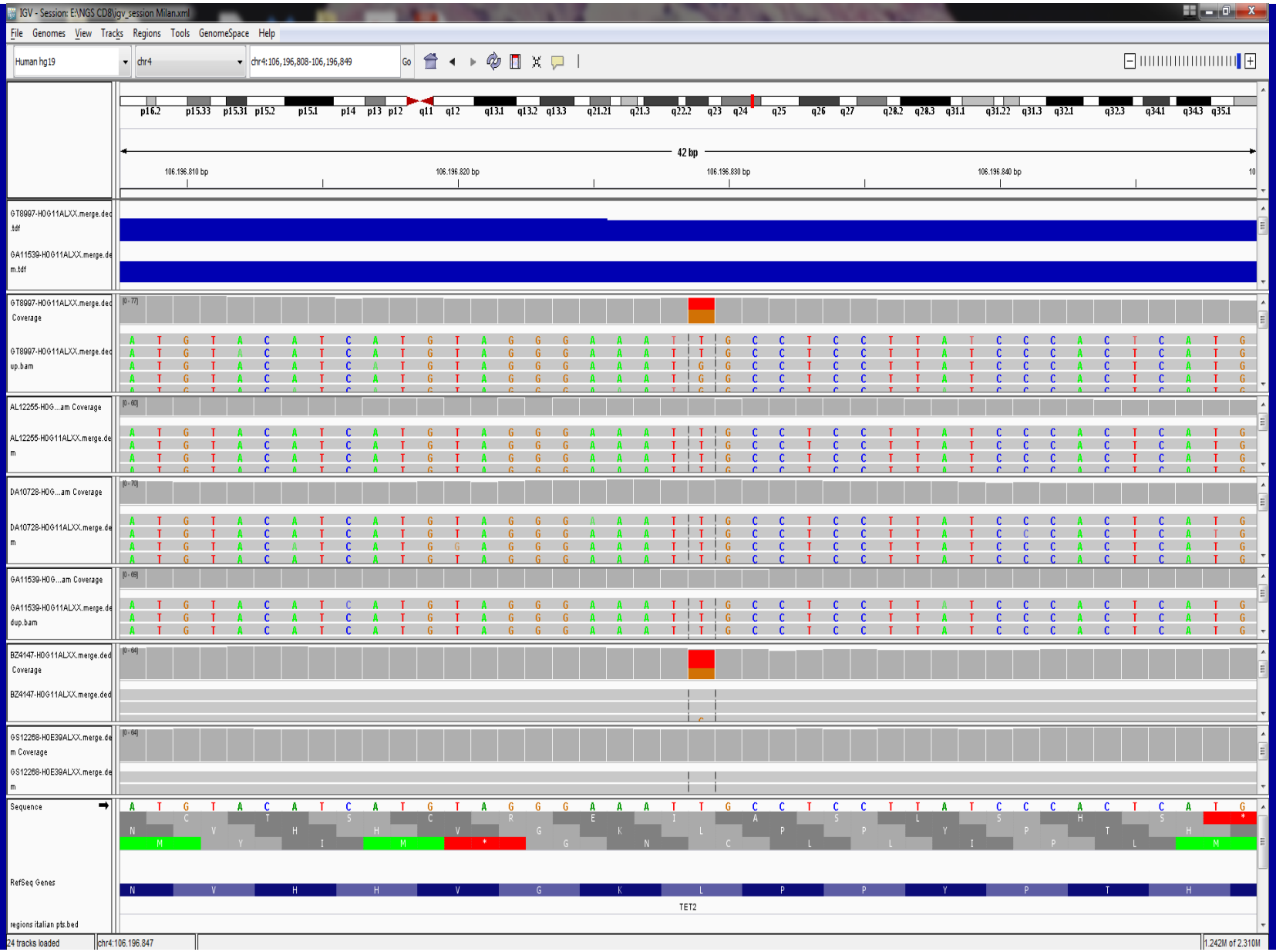
K.S.J. Elenitoba. Seminars in Diagnostic Pathology 34 (2017) 15–21

TRASLOCAZIONE
t(11; 14) (q13; q32)

NORMALE



TRASLOCATO


IGV - Session: E:\NGS CD8\igv_session Milan.xml
File Genomes View Tracks Regions Tools GenomeSpace Help
Human hg19
chr4
chr4:106,196,808-106,196,849
Go
42 bp
106.196.810 bp
106.196.820 bp
106.196.830 bp
106.196.840 bp
GT8997-H0G11ALXX.merge.ded.tdf
GA11539-H0G11ALXX.merge.dedup.tdf
GT8997-H0G11ALXX.merge.ded Coverage
GT8997-H0G11ALXX.merge.dedup.bam
AL12255-H0G...am Coverage
AL12255-H0G11ALXX.merge.dedup
DA10728-H0G...am Coverage
DA10728-H0G11ALXX.merge.dedup
GA11539-H0G...am Coverage
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BZ4147-H0G11ALXX.merge.ded Coverage
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GS12268-H0E39ALXX.merge.dedup Coverage
GS12268-H0E39ALXX.merge.dedup
Sequence
RefSeq Genes
TET2
regions italian pts.bed
24 tracks loaded
chr4:106.196.847
1.242M of 2.310M

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).

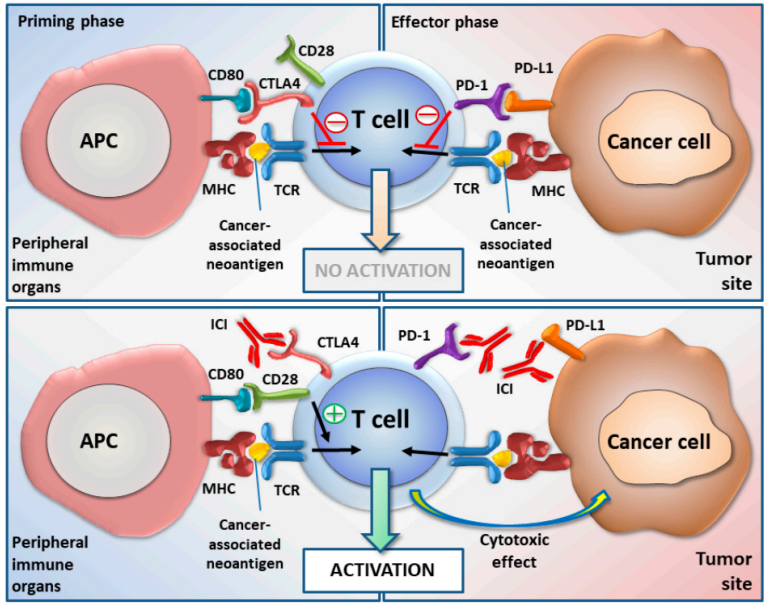
Antibody Drug Conjugated in Hematologic Malignancies

Target	Conjugate	B-Cell				T-Cell NHL	Myeloid Leukemia	Hodgkin Lymphoma
		NHL	CLL	MM	ALL			
CD3	Diphtherai Toxin A					■		
CD19	DM4	■	■		■			
CD22	Calicheamycin MMAE PE38	■	■		■			
CD30	MMAE	■				FDA approved		FDA approved
CD33	DM4 Gelonin						■	
CD56	DM1			■				
CD74	Doxorubicin			■				
CD79	MMAE	■						
CD138	DM4			■				

Leslie, L and Younes, A: ASCO 2013

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

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)

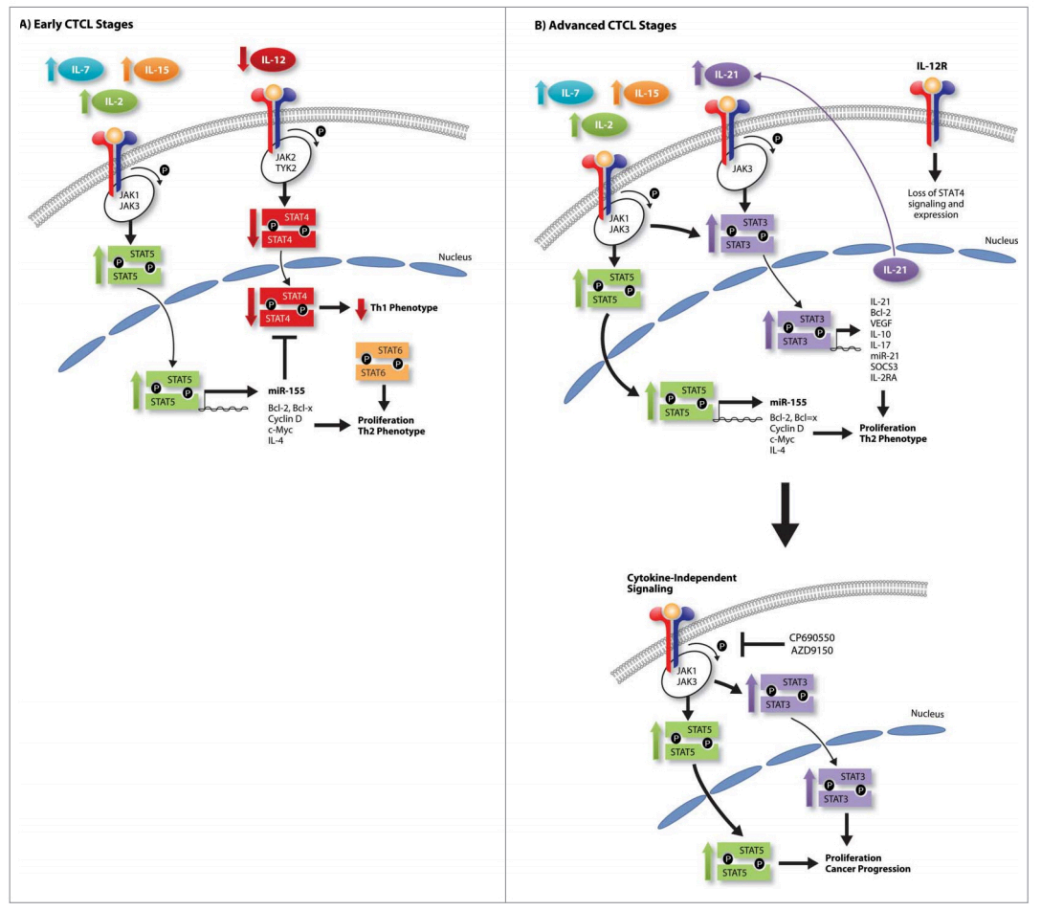
Ferenczi K, et al. J invest Dermatol 2002;119:1405

BIOMARKERS DI SUPERFICIE

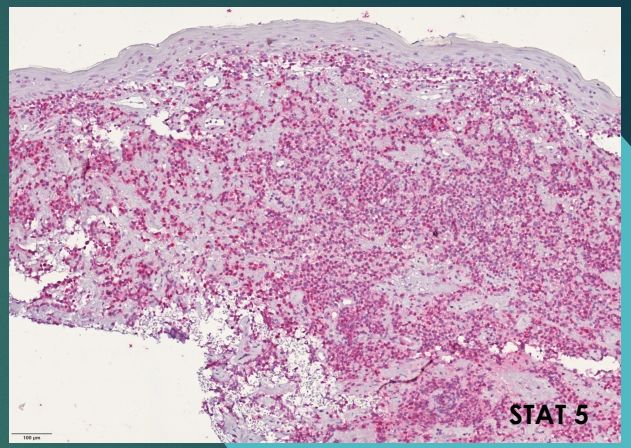
- ***KIR3DL2/CD158k***
  - Killer-cell immunoglobulin-like receptor
  - Espresso dalle NK e dalle cellule di Sézary
  - Importanza per **diagnosi** e **follow-up** della SS
  - valutazione del tumor burden
  - Diagnosi differenziali con dermatiti infiammatorie, soprattutto nelle forme di SS iniziale 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

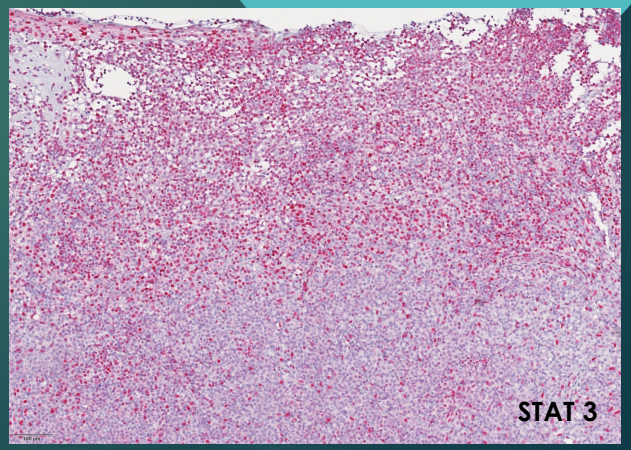
Hurabielle C, et al. Clin Cancer Res 2017.
Roelens M, et al. Blood 2017;130:1468

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

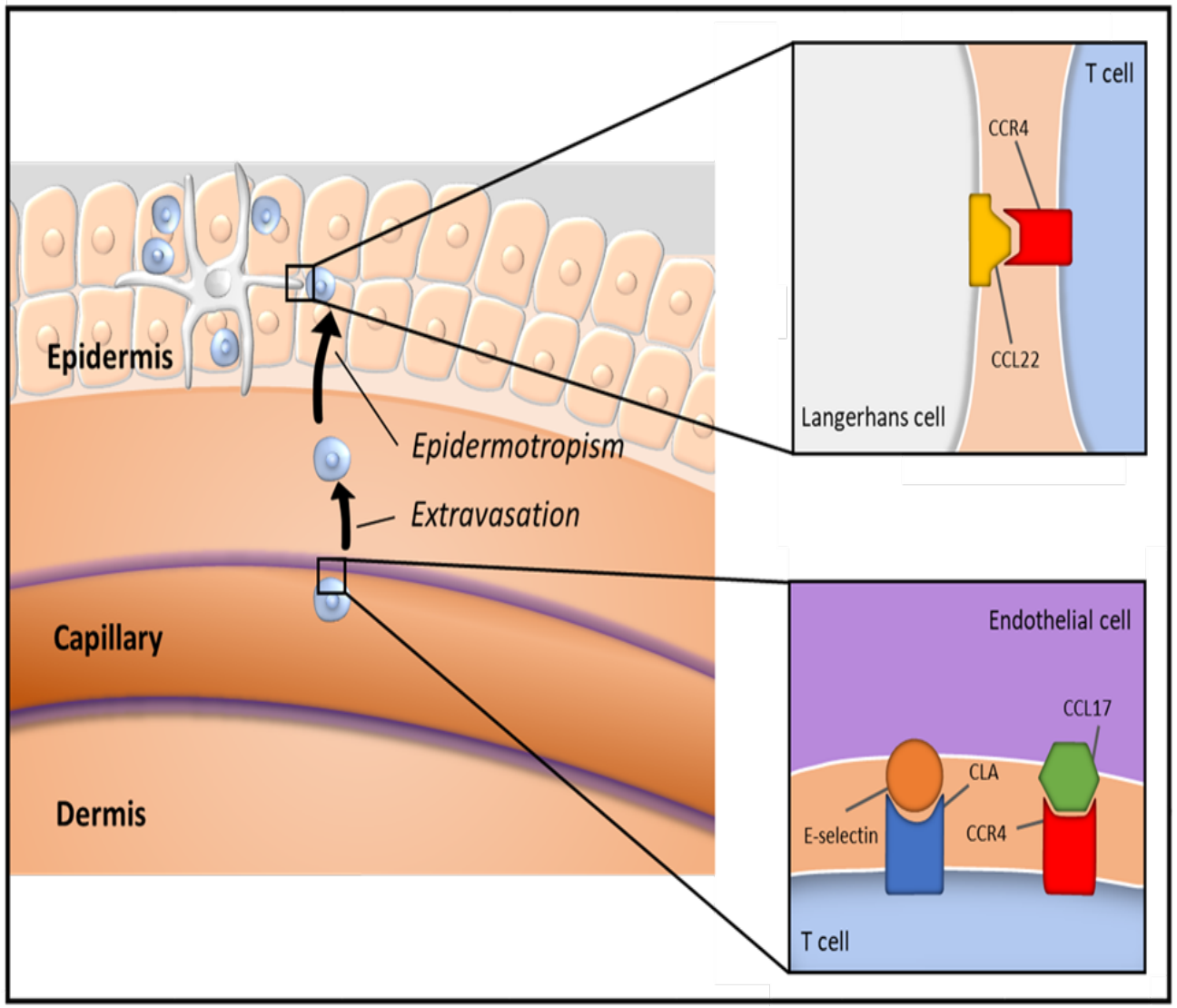
J Eur Acad Dermatol Venereol. 2017 Jan;31(1):e27-e29. doi: 10.1111/jdv.13597. Epub 2016 Mar 3.

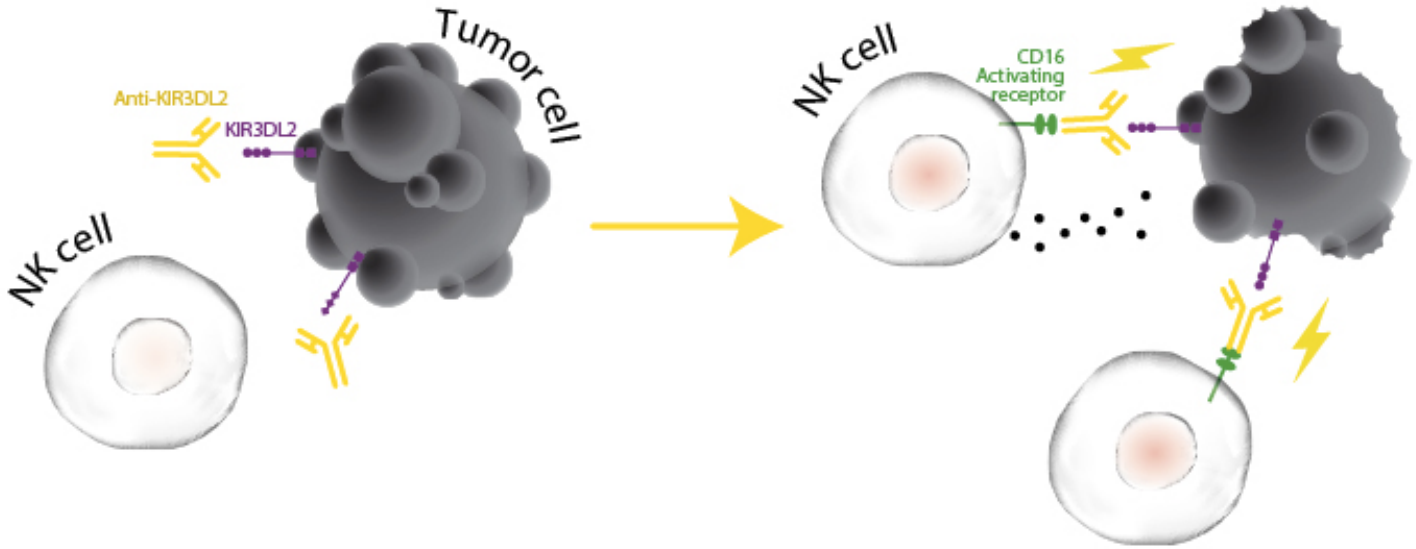
miR-155 expression in Primary Cutaneous T-Cell Lymphomas (CTCL).

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**


Epidermis
Capillary
Dermis
Epidermotropism
Extravasation
T cell
CCR4
CCL22
Langerhans cell
Endothelial cell
CCL17
CLA
E-selectin
CCR4
T cell


Tumor cell
Anti-KIR3DL2
KIR3DL2
NK cell
NK cell
CD16
Activating
receptor
IPH4102 binds to KIR3DL2
on tumor cells
Recruitment of NK cells
and depletion of tumor cells