Webinars

Cutaneous Lymphoma

EuroBloodNet Topic on Focus

Indolent Primary Cutaneous B-cell lymphomas

Prof Emmanuella Guenova
Lausanne University Hospital
University of Lausanne
Lausanne, Switzerland

Prof Pablo L Ortiz-Romero
Hospital 12 de Octubre
Complutense University
Madrid, Spain

26.10.2020

Co-funded by the Health Programme of the European Union

UNIL | Université de Lausanne

Hospital Universitario 12 de Octubre SaludMadrid

Universidad Complutense Madrid

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

No conflicts of interest

Learning objectives

1. Primary cutaneous marginal zone lymphoma
2. Primary cutaneous follicle center lymphoma
3. Lymphoma mimickers

Primary cutaneous lymphomas

- Group of lymphoid neoplasias
- Initial presentation, skin
- No extracutaneous involvement at diagnosis

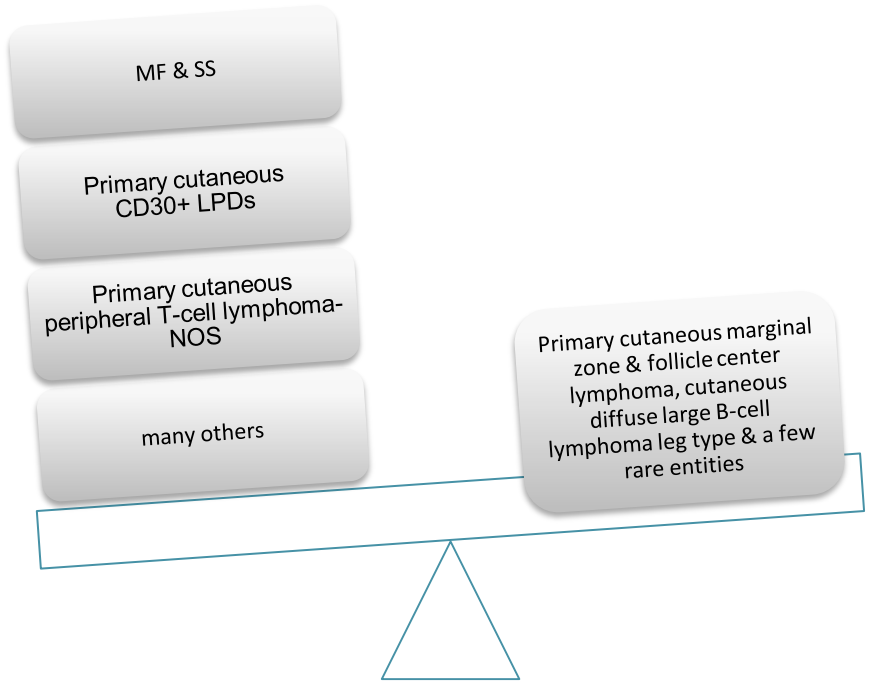
- Epidemiology
  - Incidence, around 1/100.000
  - 75-80%, T-cells
  - 20-25%, B-cells

- Some of them same names/morphology as systemic lymphomas

- Different diseases. Different treatment

pcCTCL 75-80%

pcCBCL 20-25%



1. Swerdlow SH, et al. Blood 2016;127:2375–90; 2. Willemze R, et al. Blood. 2019 Sep 26;134(13):1112; 3. Swerdlow SH IARC Press; 7 Sept 2017: ISBN-13 (Print Book); 4. R La Selva et al. Indian J Dermatol. 2017 Mar-Apr; 62(2): 146–157

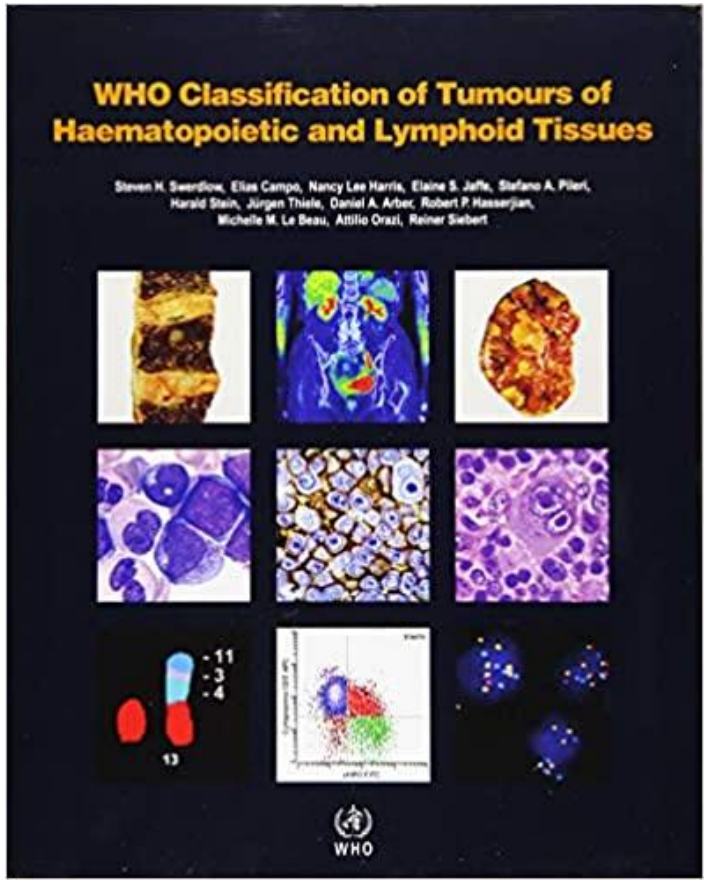
Primary cutaneous B-cell lymphomas

CME Article

The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas

Rein Willemze,[1] Lorenzo Cerroni,[2] Werner Kempf,[3] Emilio Berti,[4] Fabio Facchetti,[5] Steven H. Swerdlow,[6] and Elaine S. Jaffe[7]

	Frequency	5-year survival
pc marginal zone lymphoma*	9%	99%
pc follicle center lymphoma	12%	95%
pc diffuse large B-cell lymphoma leg type	4%	56%
EBV+ mucocutaneous ulcer$_{(provisonal)}$	<1%	100%
Intravascular large B-cell lymphoma	<1%	72%

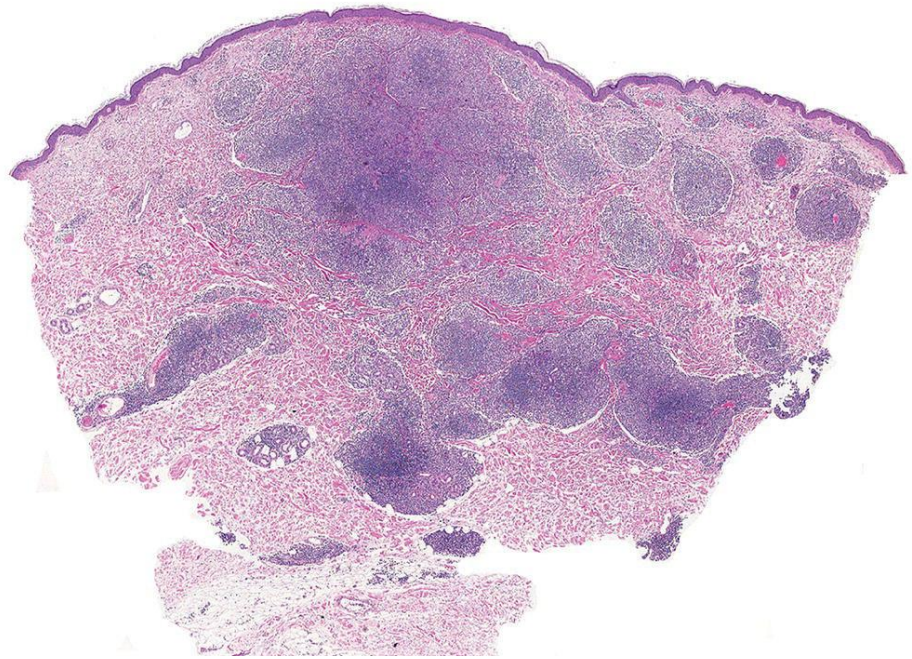


*extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

1. Swerdlow SH, et al. Blood 2016;127:2375–90; 2. Willemze R, et al. Blood. 2019 Sep 26;134(13):1112; 3. Swerdlow SH IARC Press; 7 Sept 2017: ISBN-13 (Print Book)

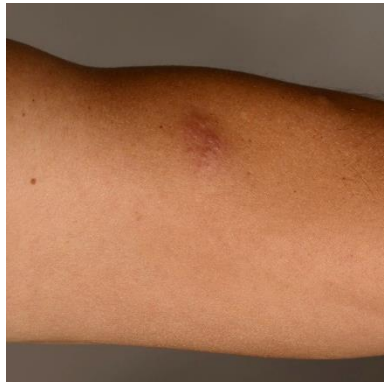
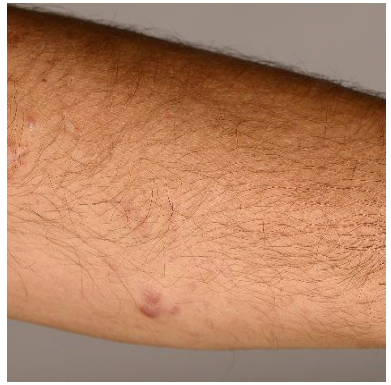
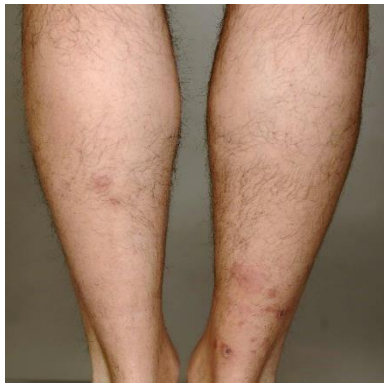
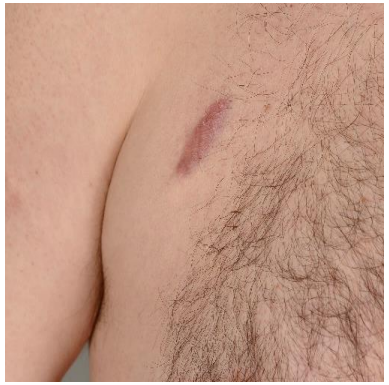
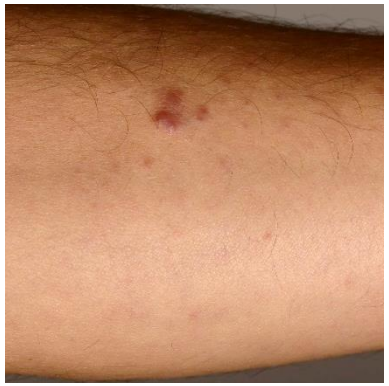
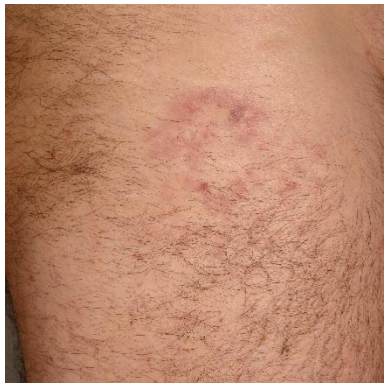
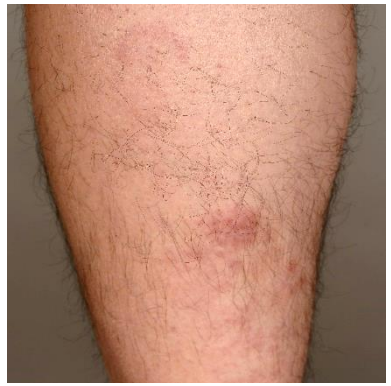
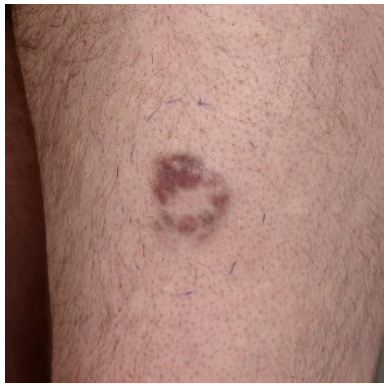
Primary cutaneous marginal zone lymphoma | PCMZL

- Definition
  - lacks extracutaneous involvement at diagnosis
  - does not fulfill criteria for any other small B-cell lymphoma
- History
  - Includes cases previsouly diagnosed as
    - Immunocytoma (1997 EORTC classification)
    - Non-myelomatous plasmocytoma of the skin
- Epidemiology
  - 25-30% of all CBCL | 7% of all primary CL
  - M>F, median age in the 5th and 6th decade
    - Can occur in children
- <u>Excellent prognosis</u>
  - 99% 5-year survival rate



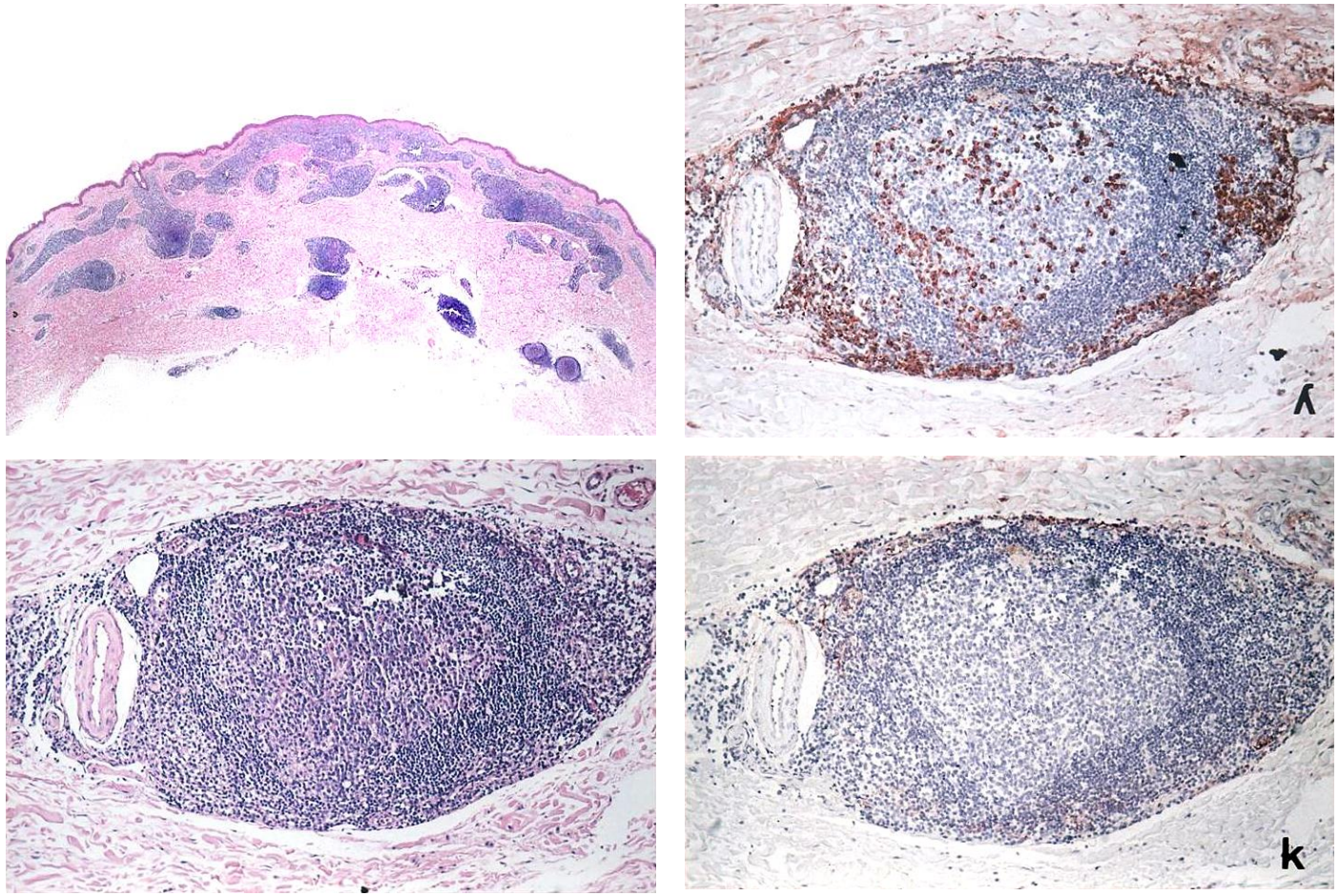
1. Swerdlow SH, et al.Semin Diagn Pathol. 2017 Jan;34(1):76-84.; 2. Willemze R, et al. Blood. 2019 Sep 26;134(13):1112; 3. Cerroni L. Skin Lymphoma: The Illustrated Guide, 5th Edition ISBN: 978-1-119-48590-2, 2020 Wiley-Blackwell (Print Book)

- Clinical presentation
  - subtle to erythematous to violaceous macules, papules, plaques and/or nodules
  - arms, trunc >> head & neck region (30%), seldom legs
  - solitary or multifocal, sometimes widely distributed
  - Rare aggminated or anetodermic forms

Primary cutaneous marginal zone lymphoma | histology

- Morphology
  - Patchy, nodular or diffuse infiltrates
  - Reactive germinal centers
  - Plasma cells
  - Reactive lymphocytes
- Immunohistochemistry
  - CD20+, CD79+, bcl-2+, IRTA+
  - CD5-, CD10-, bcl-6-, cyclin-D1-
- Subtypes
  - Class-switched: IgM-/CXCR3-
  - Non class-switched: IgM+/CXCR3+
- Molecular pathology
  - Monoclonal IgH rearrangement 50-60%[1-2]



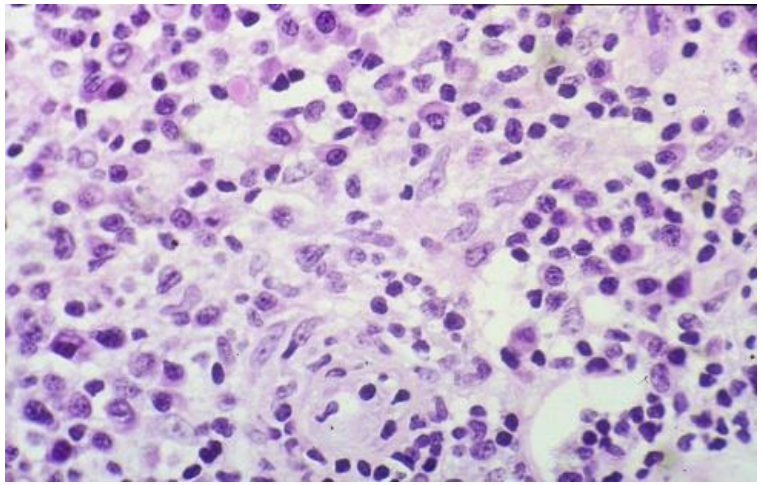
1. .van Maldegem F et al. *Blood*. 2008;112:3355–3361; 2. Edinger JT et al. *Am J Surg Pathol*. 2010;34:1830–1841.; 3. Swerdlow SH, et al.Semin Diagn Pathol. 2017 Jan;34(1):76-84.; 4. Cerroni L. Skin Lymphoma: The Illustrated Guide, 5th Edition ISBN: 978-1-119-48590-2, 2020 Wiley-Blackwell (Print Book)

Primary cutaneous marginal zone lymphoma | genetics

Somatic mutation

72%

Bcl10 (3%)
Fas
PAX5
RhoH/TTF
cMYC
PIM1



20-40%

Amplifications

Bcl2 (cr18)
FoxP1 (cr3)

Translocations

24%

t14;18
IgH-MALT1

0-10%

t(14;18)
(q32;q21)
IgH-bcl2

0-10%

t(3;14)(p14;q32)
IgH-FoxP1

0-5%

t11;18
(q21;q21)
AP12-MALT1

1. Huh SJ et al .Oncol Lett. 2020 20(5):205; 2. Streubel B et al. Blood 2003 101:2335–2339; 3. Palmedo G et al. Am J Dermatopathol 200; 29:231–236; 4. Streubel B et al. Leukemia 200; 19:652–658.; . 5. Gallardo F et al. Hum Pathol 2006 37:867–87 ; 6. Maurus K et al. J Invest Dermatol 2018 138(7):1573-1581

Primary cutaneous marginal zone lymphoma | recommendations for staging evaluations

Complete clinical examination

Skin biopsy

Imaging

- CT and/or FDG-PET scans

Laboratory studies

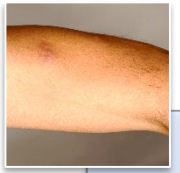
- Complete differential blood count
- Blood chemistry (incl LDH)
- *B. burdorferi* serology
- Serum electrophoresis

Bone marrow biopsy

- not required unless indicated by other staging assessments

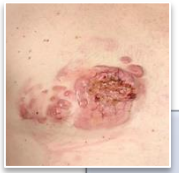
1. Kim Y et al. Blood 2007 Jul 15;110(2):479-84.; . Senff NJ et al. Blood. 2008;112:1600–9. 2. Dippel, E., et al. J Dtsch Dermatol Ges 2018 16(1): 112-123.; 3. Willemze, R., et al. Ann Oncol 2018 29 (Supplement_4) iv30-iv40;

Primary cutaneous marginal zone lymphoma | treatment



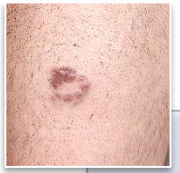
Skin directed

- Wait & see
- Radiotherapy
- Surgical excision
- Steroids
- Rituximab
- Interferon-alpha



Systemic

- Antibiotics
- Rituximab
- Interferon-alpha



Experimental

- Modified viruses
- PDT
- TLR-agonists

1. Senff NJ et al. Blood. 2008;112:1600–9. 2. Dippel, E., et al. J Dtsch Dermatol Ges 2018 16(1): 112-123.; 3. Willemze, R., et al. Ann Oncol 2018 29 (Supplement_4) iv30-iv40; 4. Moti et al J Am Acad Dermatol. 2006 Mar;54(3):524-6. doi: 10.1016/j.jaad.2005.10.016.; 5. Urosevic et al. J Clin Invest. 2007 Oct 1; 117(10): 2834–2846.

Primary cutaneous follicle center lymphoma | PCMZL

PC Follicular Center Lymphoma

12% all cutaneous lymphomas

M/F: 1.5/1, middle aged.

Clinical (1st pillar)

Plaques/nodules/tumours. Papules surrounding

Single/grouped

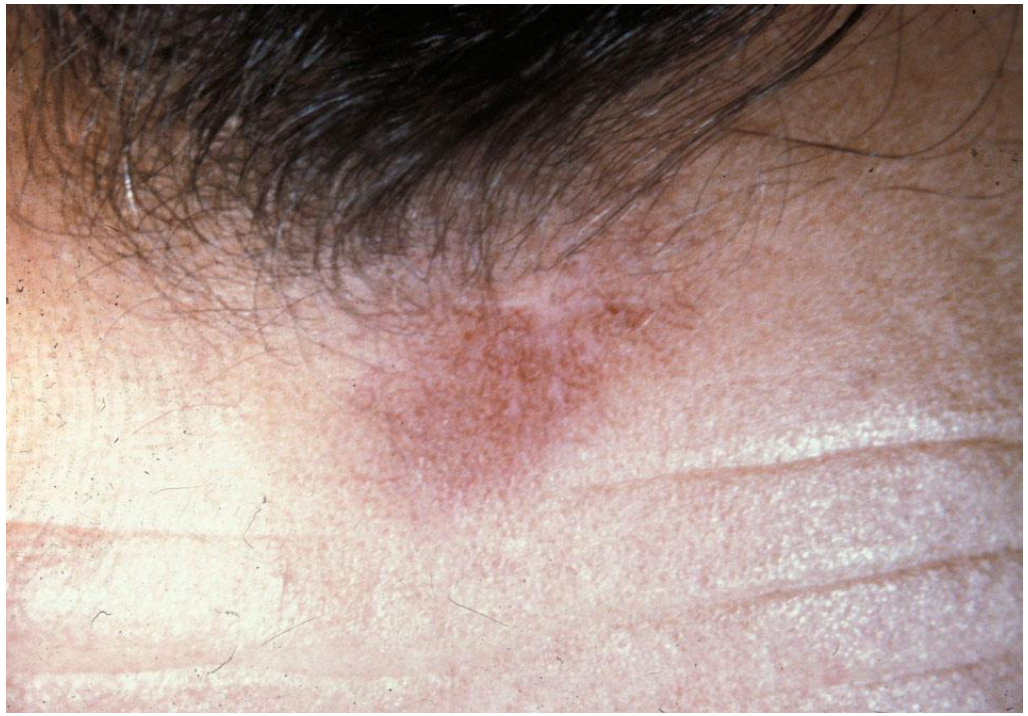
Red-violaceous. Non ulcerated (usually)

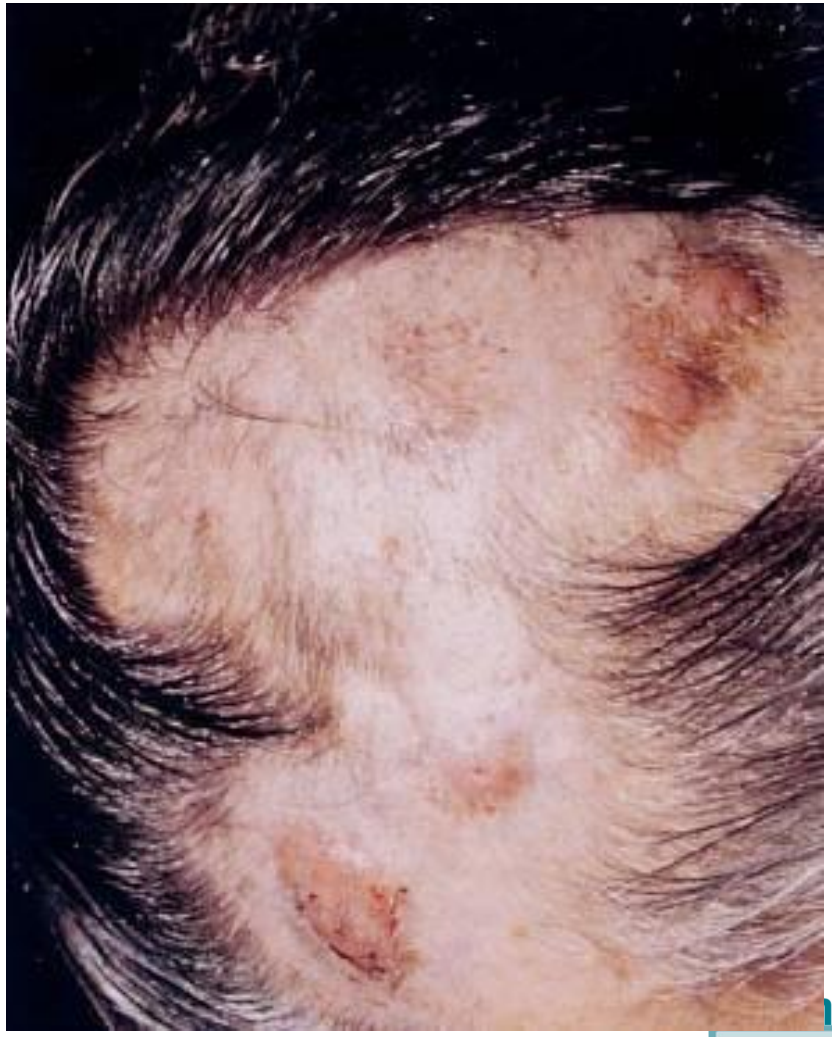
Head/back

Rare extracutaneous dissemination (5-10%)

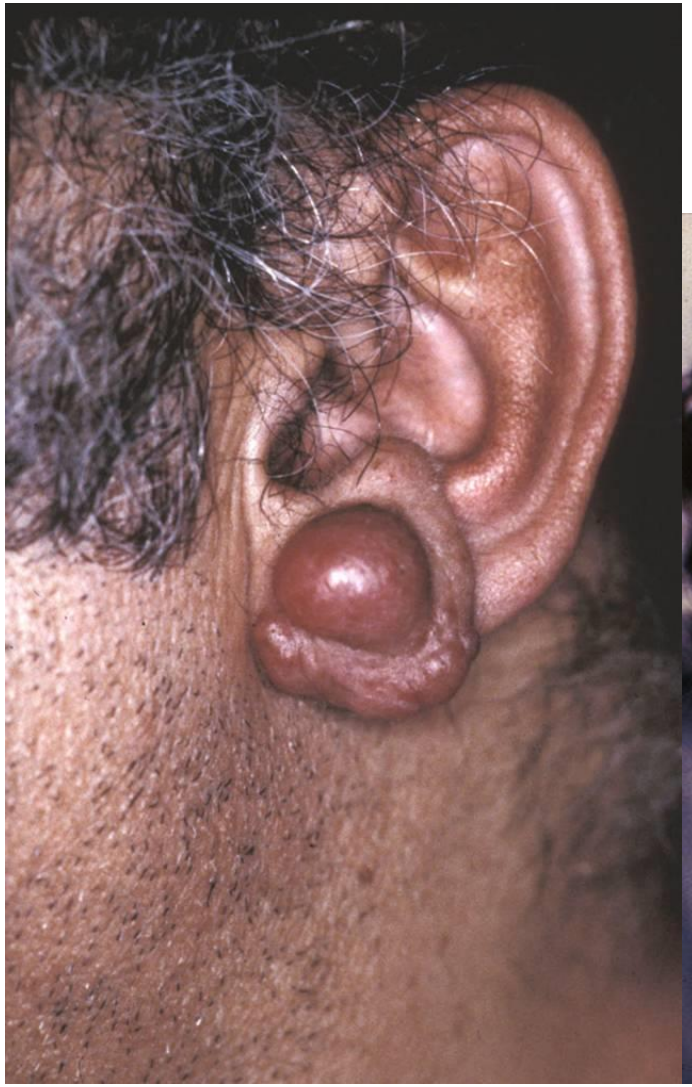
5y survival: 95%

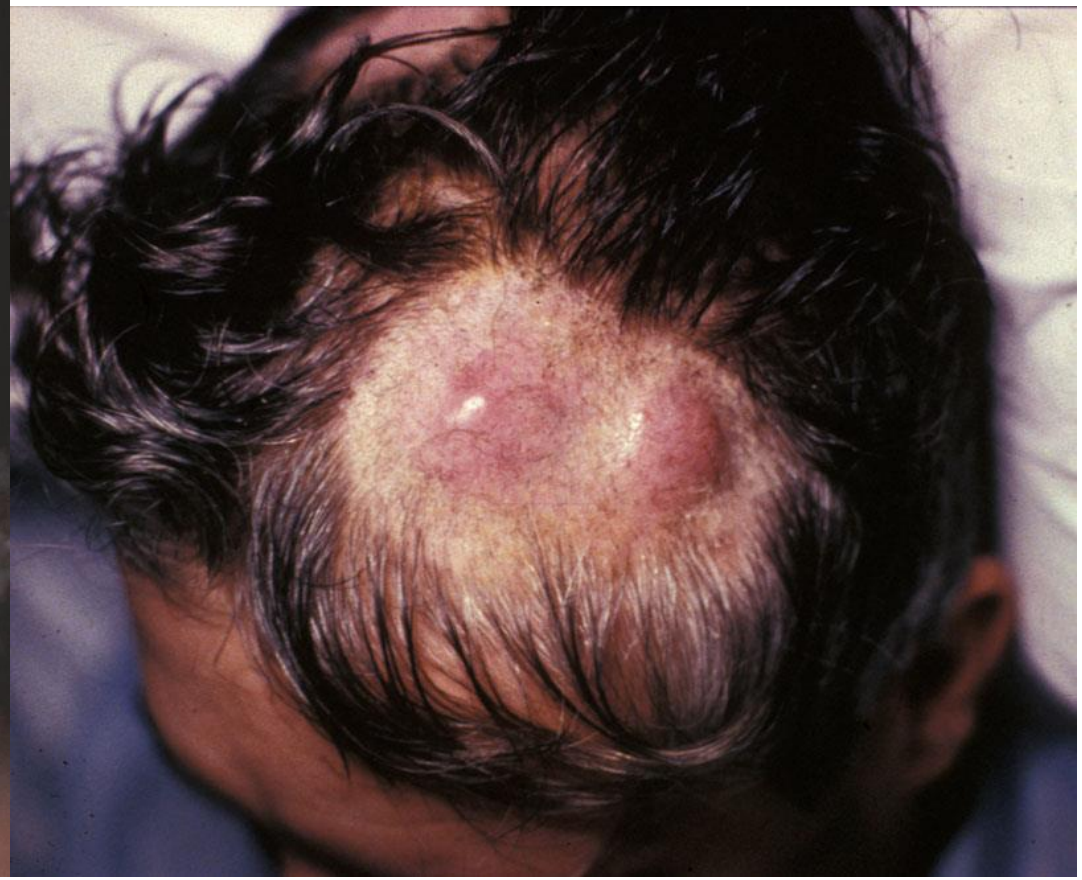
PC Follicular Center Lymphoma



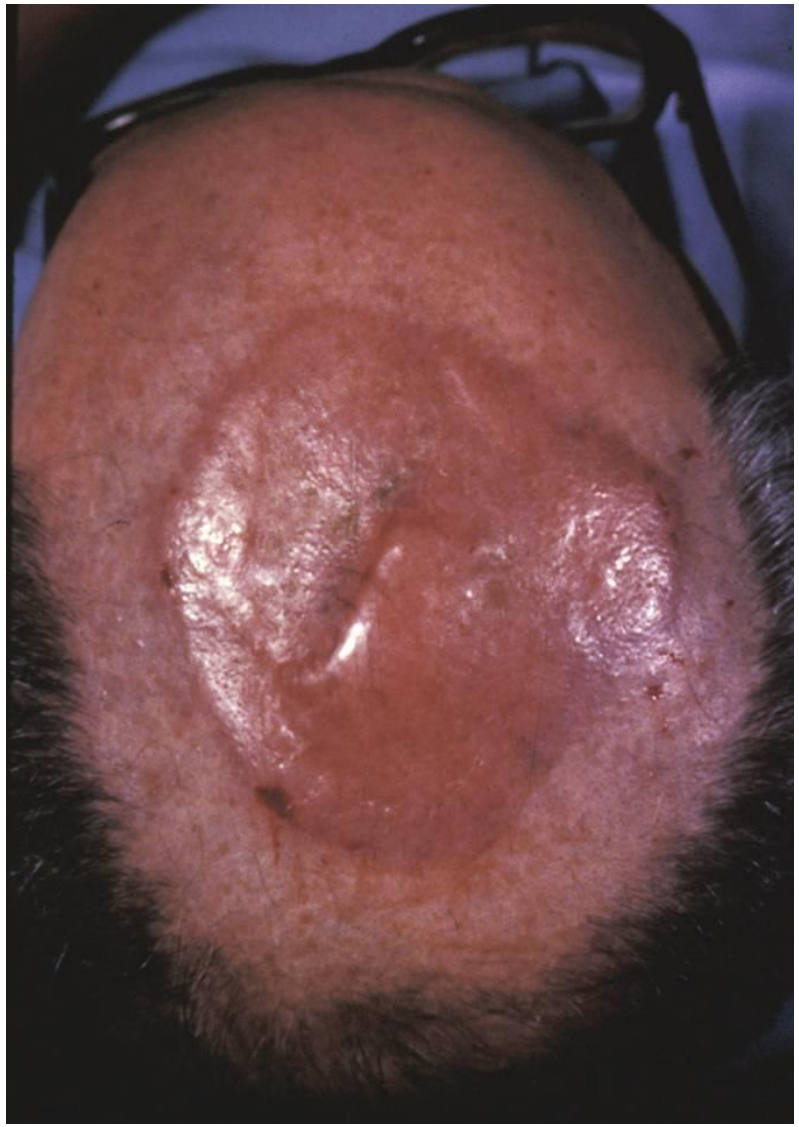


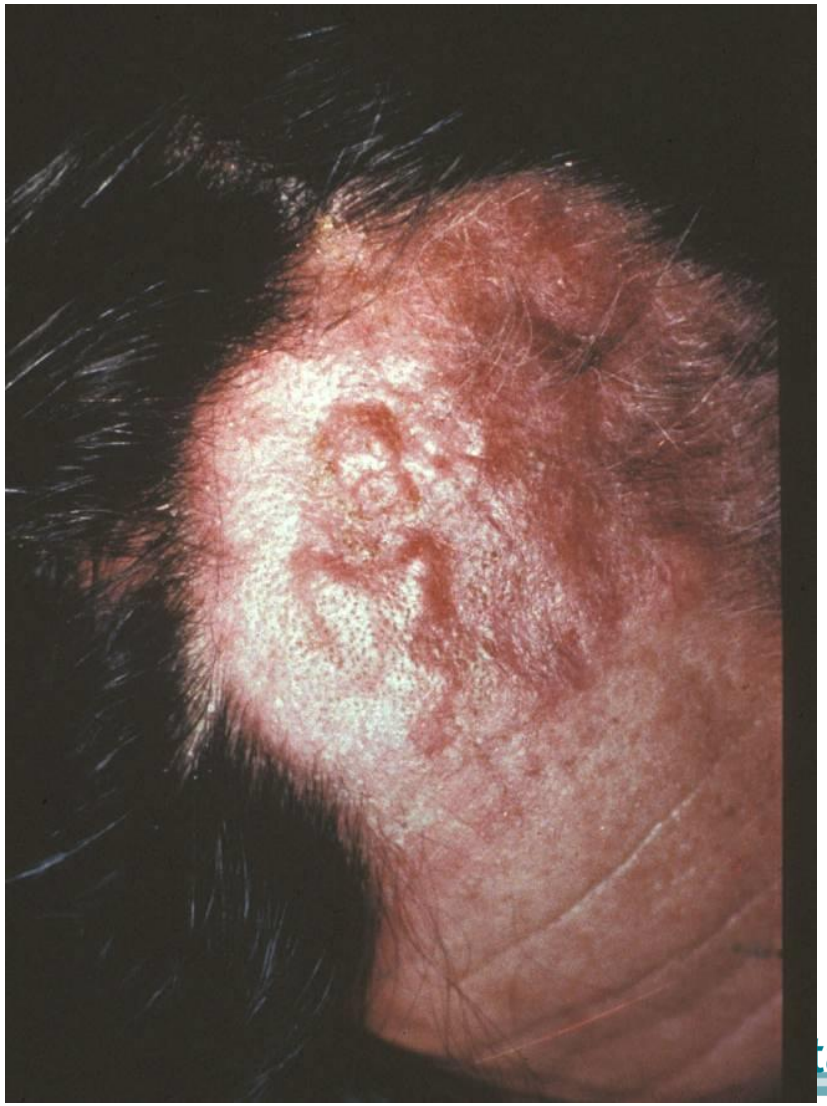
PC Follicular Center Lymphoma





PC Follicular Center Lymphoma

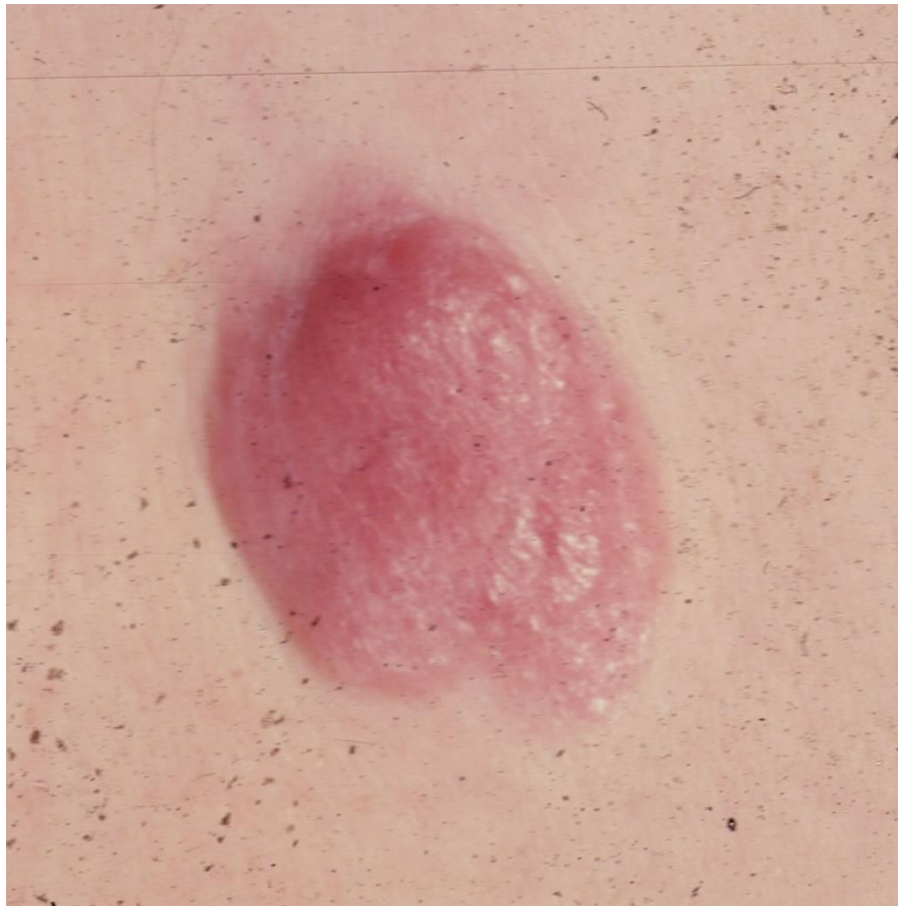


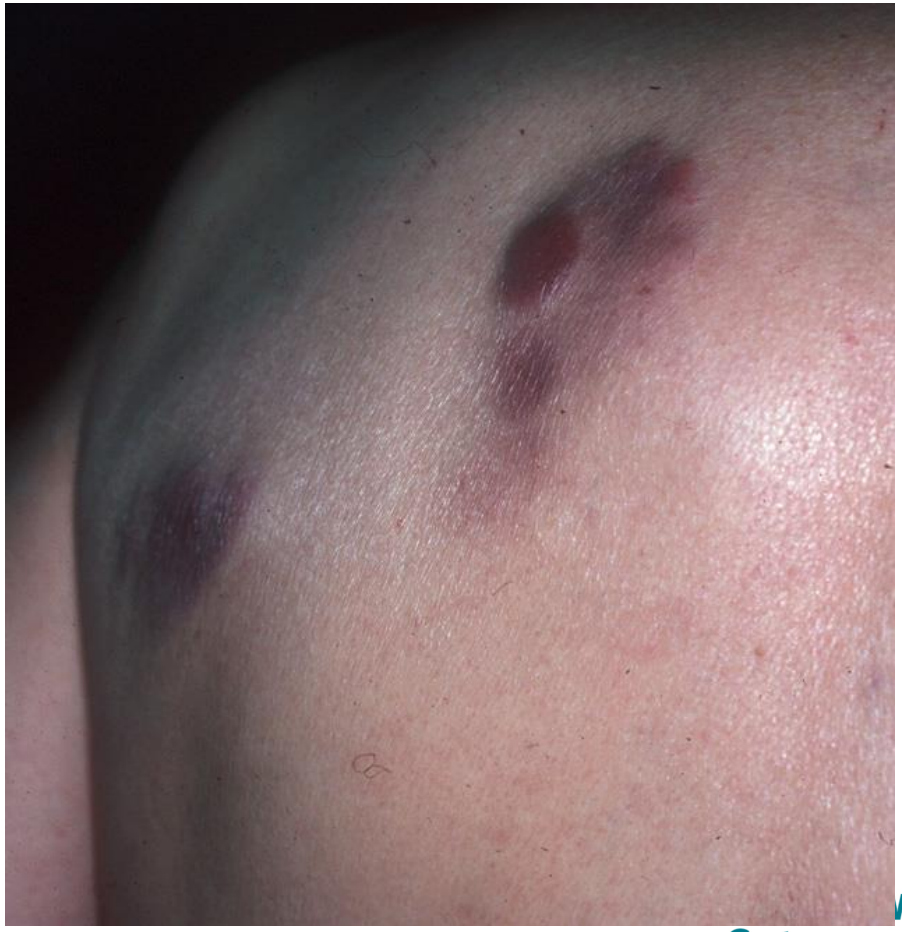


European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

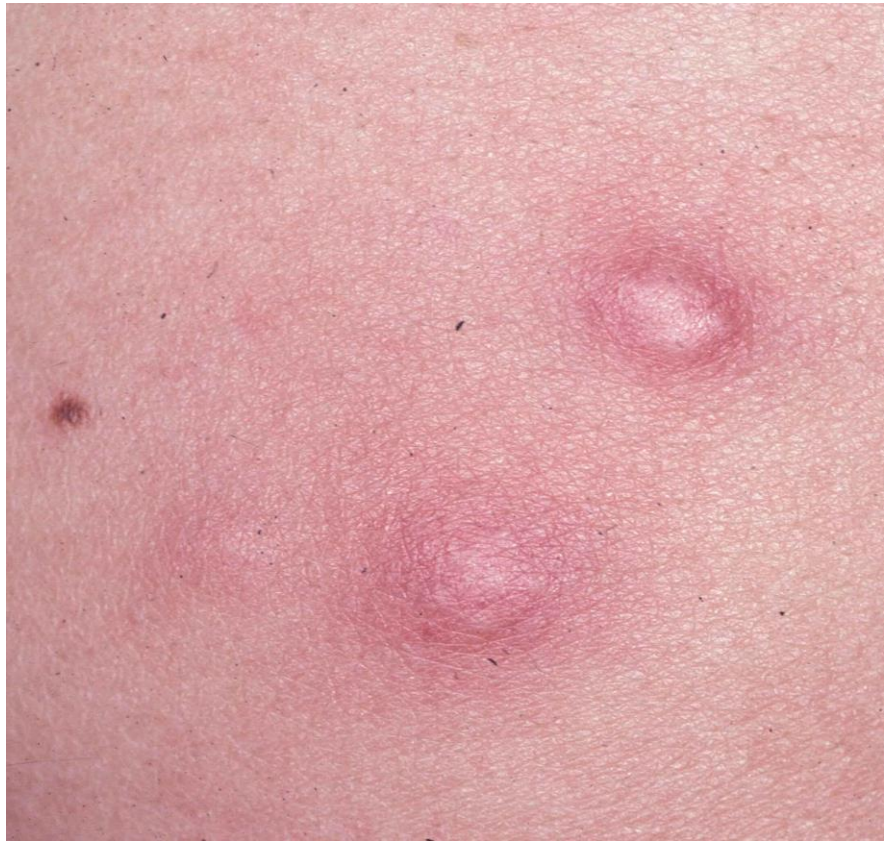
Webinars
taneous Lymphoma
EuroBloodNet Topic on Focus

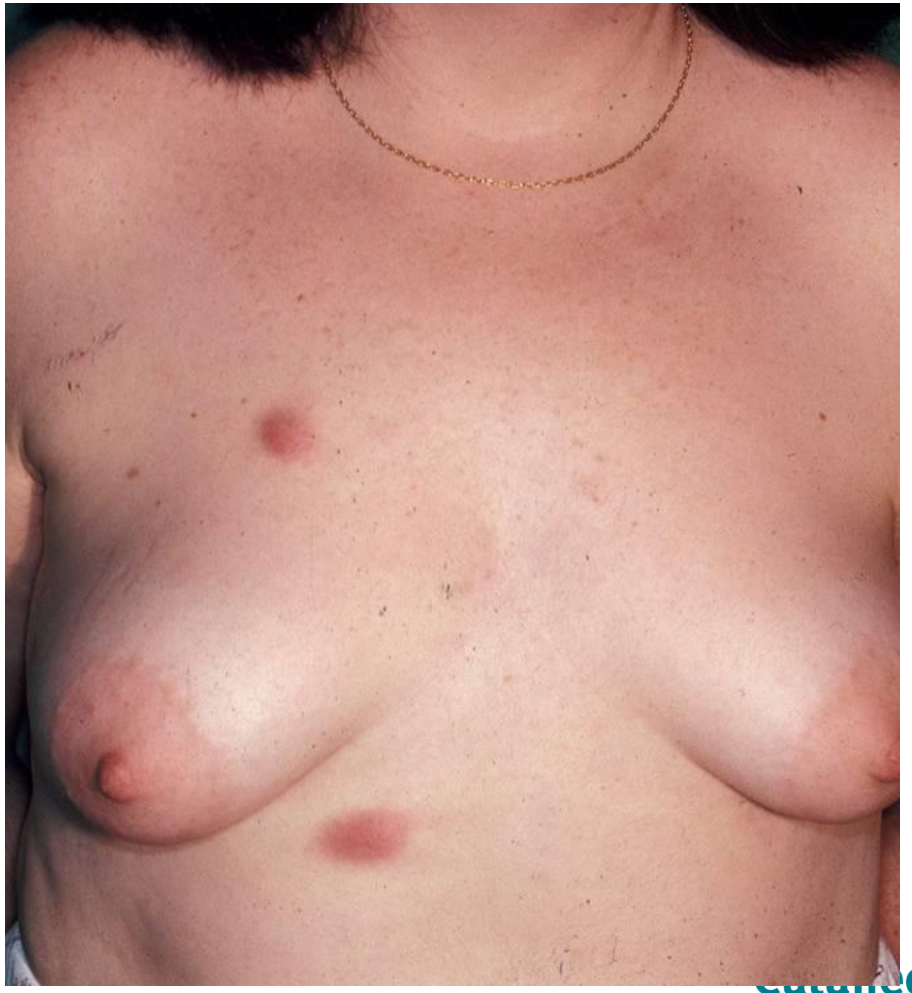
PC Follicular Center Lymphoma



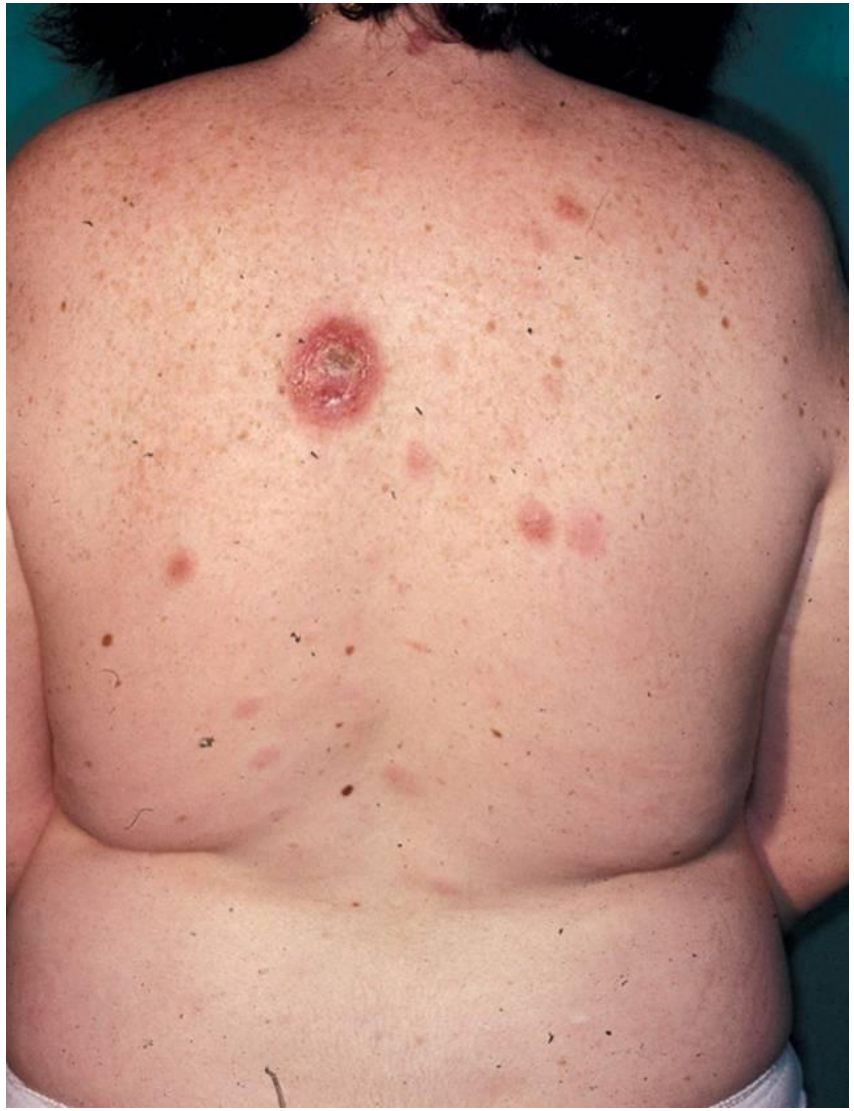


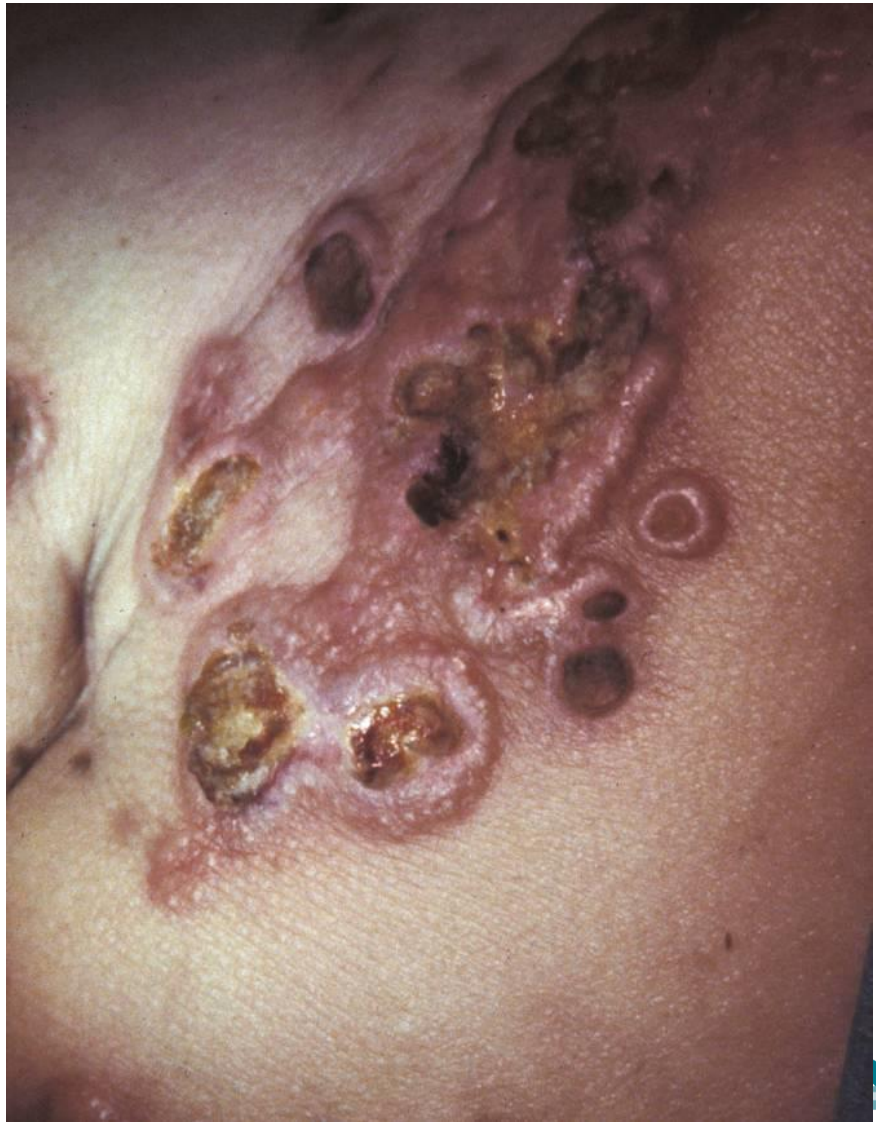
PC Follicular Center Lymphoma



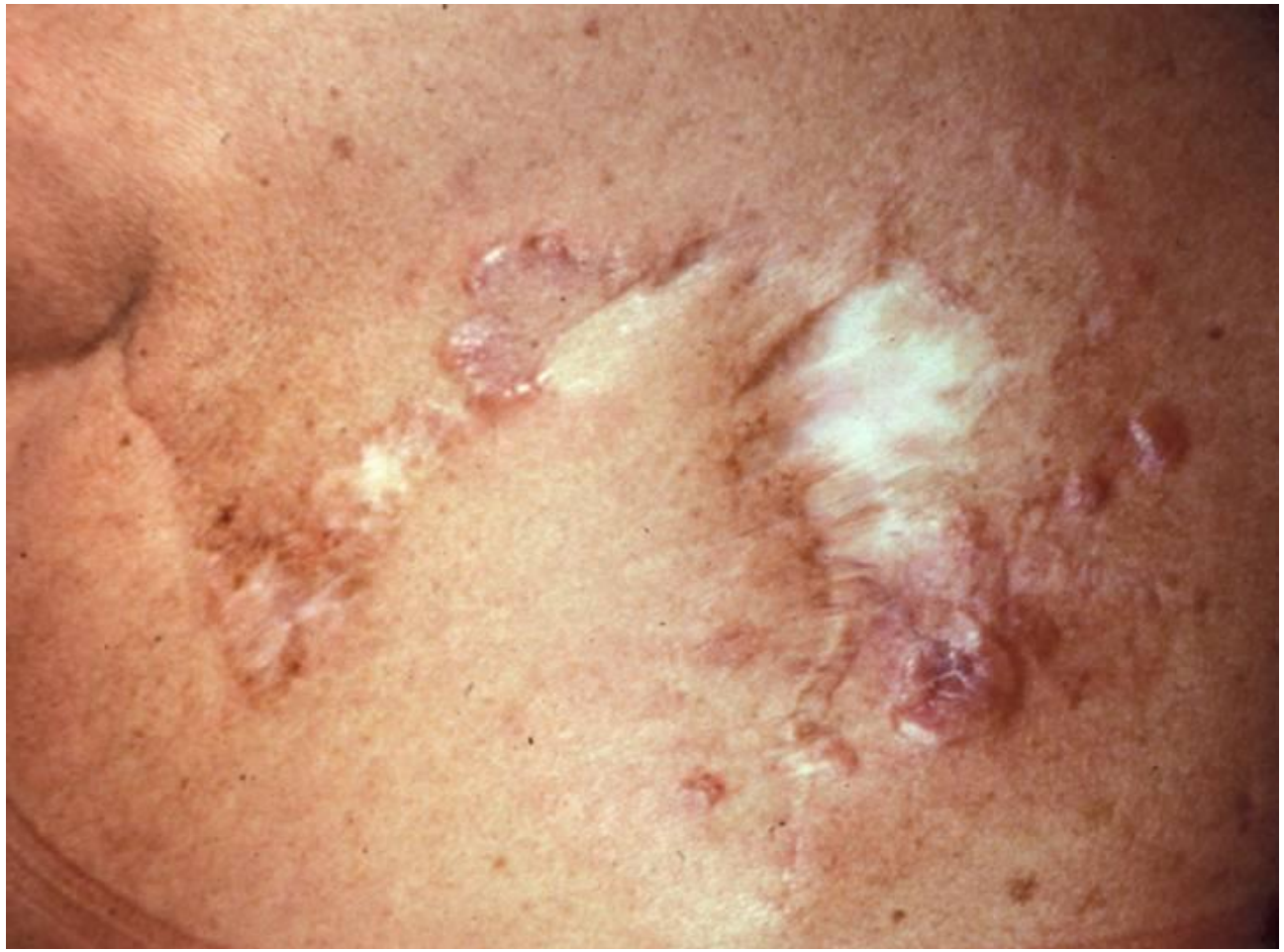


PC Follicular Center Lymphoma





PC Follicular Center Lymphoma



Reticulohistiocytoma of the dorsum; Crosti lymphoma

PC Follicular Center Lymphoma

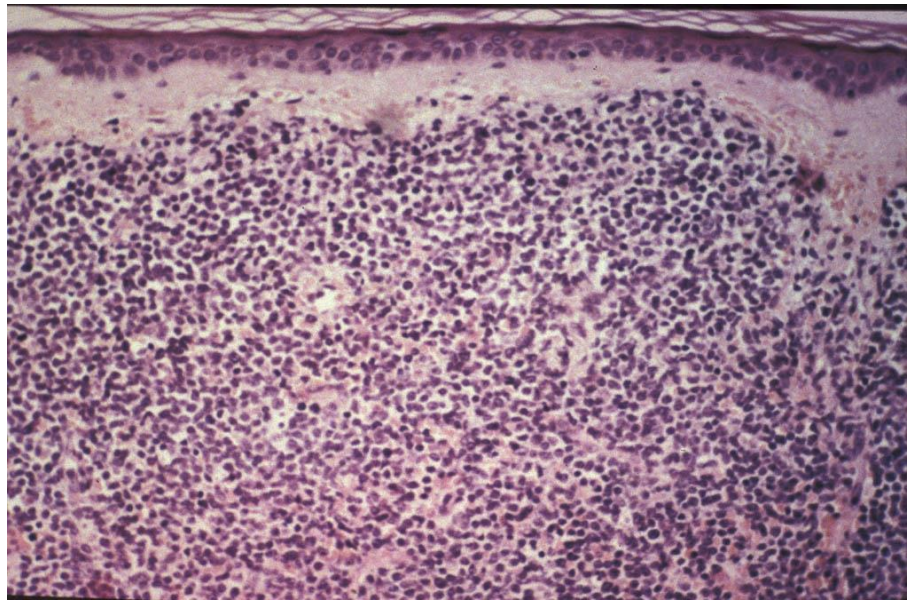
Histopathology (2nd pillar)

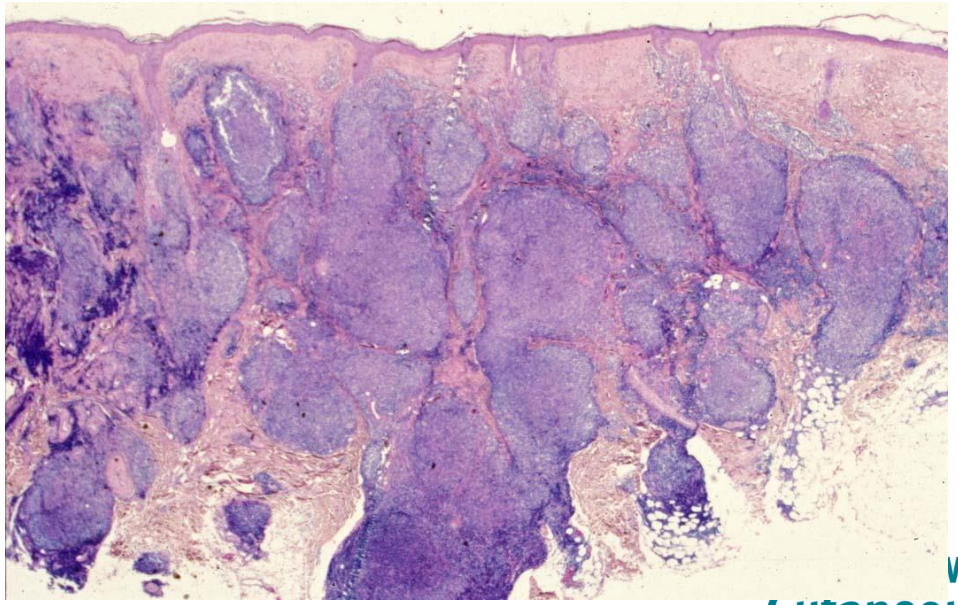
Follicular (more frequent on scalp and early lesions)

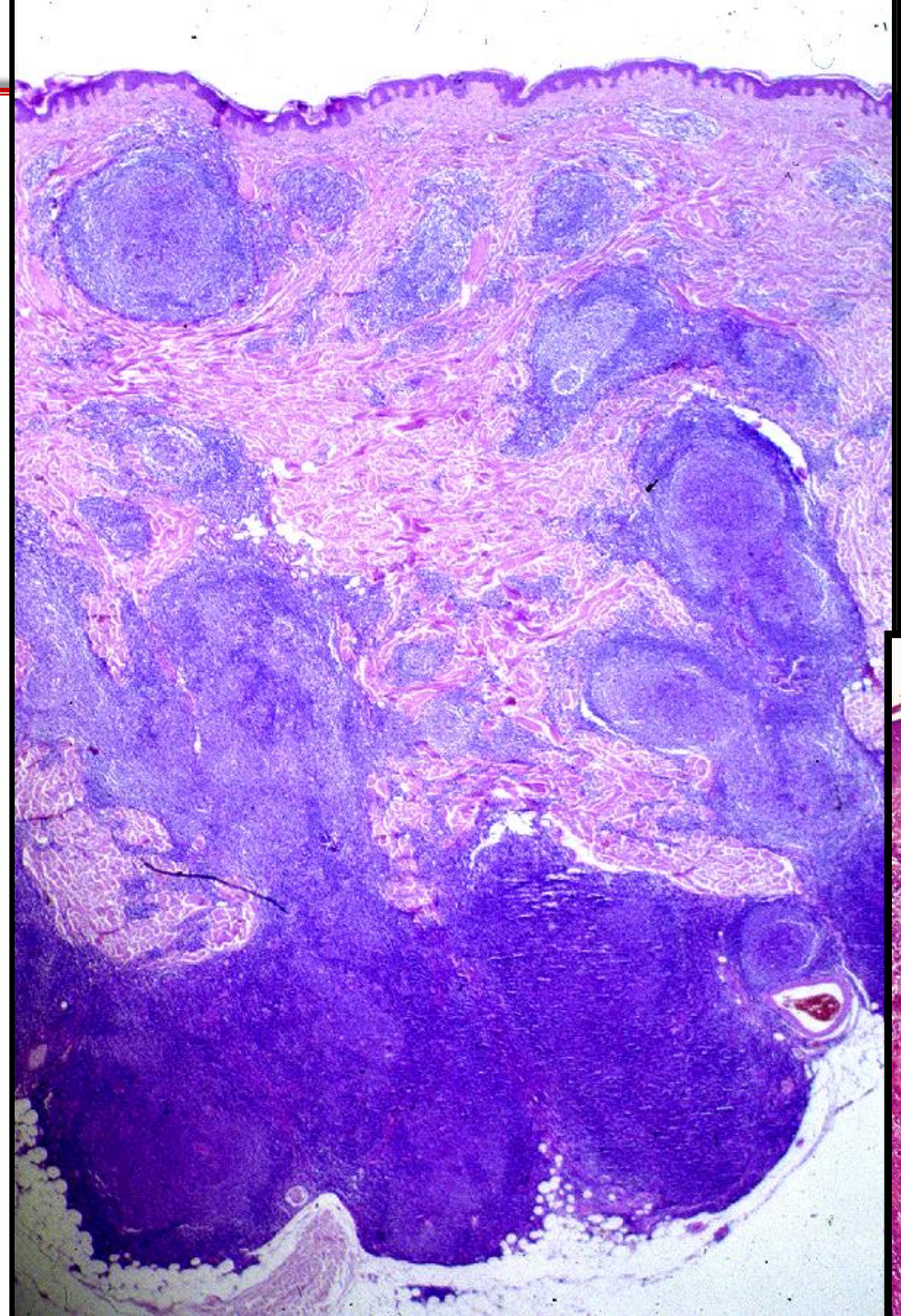
diffuse or mixed

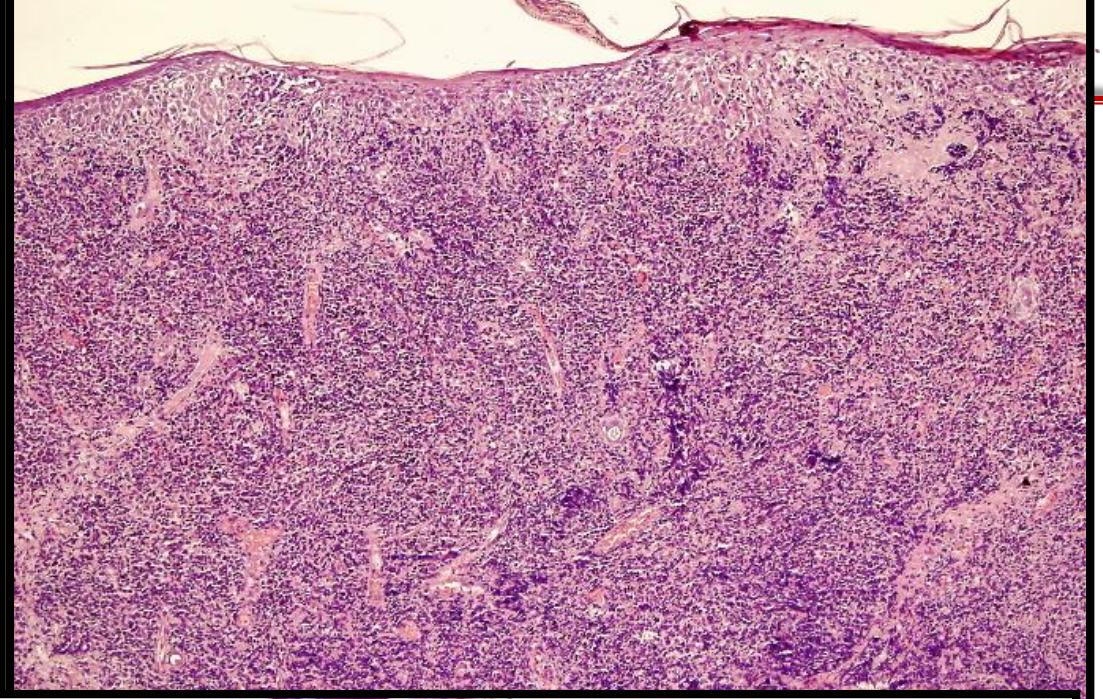
Grenz zone

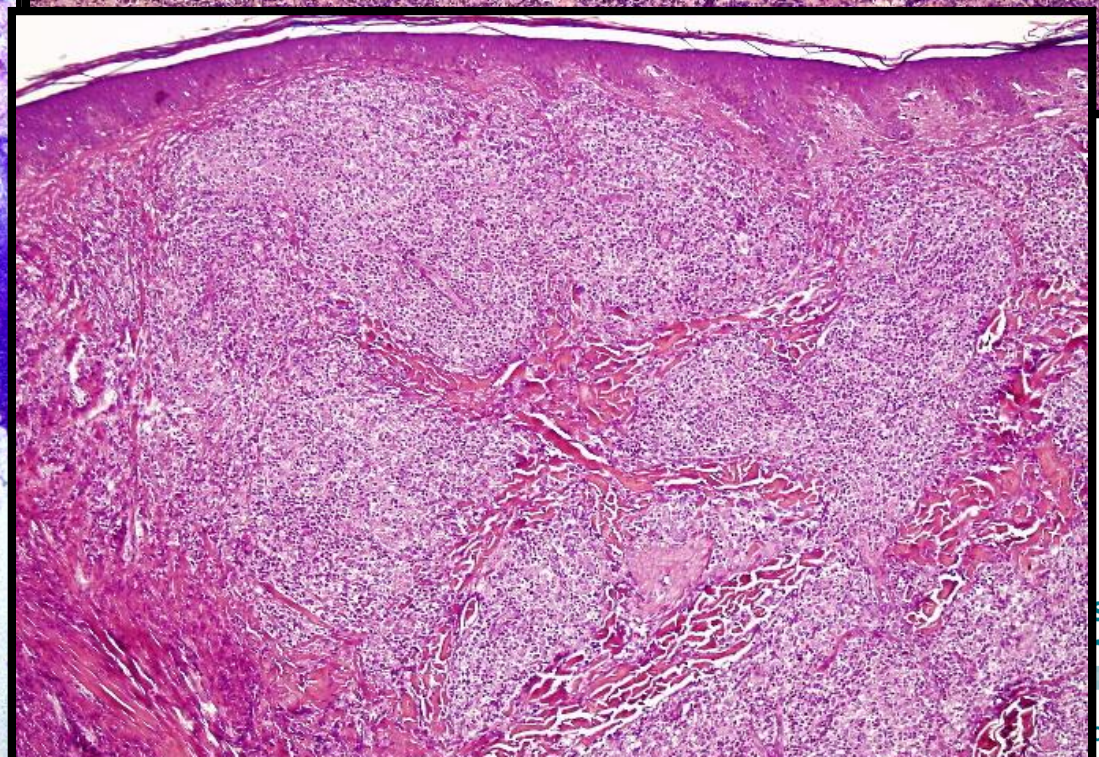
Centrocytes/centroblasts mix









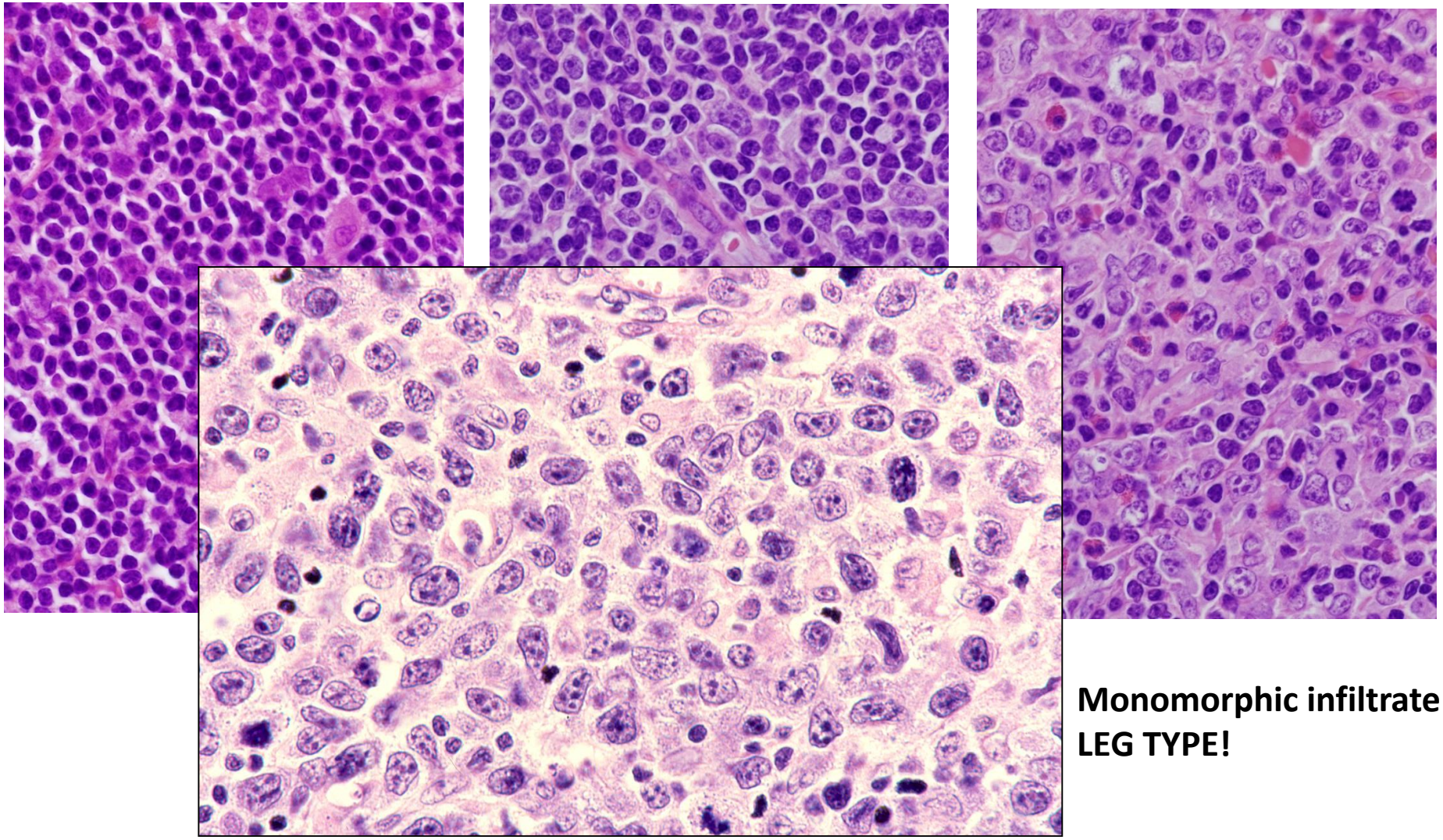


European Reference Network
for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

s
mphoma
t on Focus

PC Follicular Center Lymphoma



Monomorphic infiltrate
LEG TYPE!

PC Follicular Center Lymphoma

Inmunohistochemistry (3rd pilar)

CD 19, CD20, CD22, CD79A+

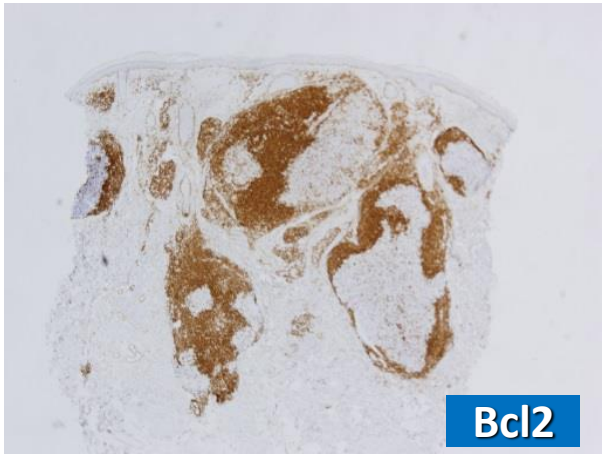
CD5 -,

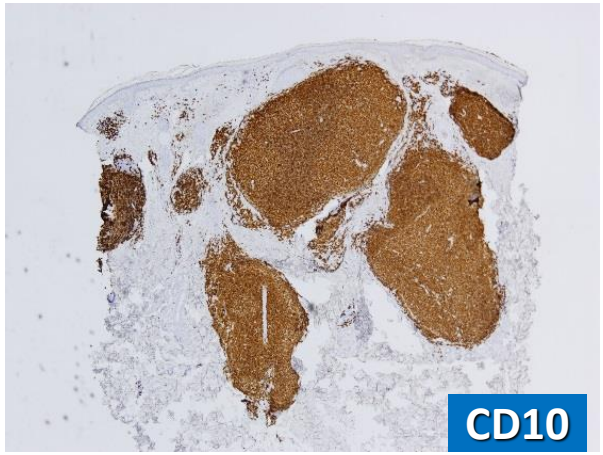
Bcl2-, bcl6+, CD10+ (follicular) o – (diffuse),

IRF4/MUM1-, FOXP1 -.

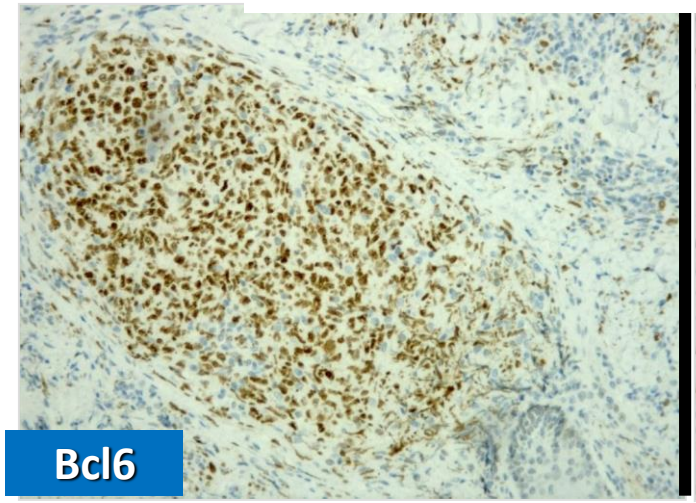
IgS+ monoclonal

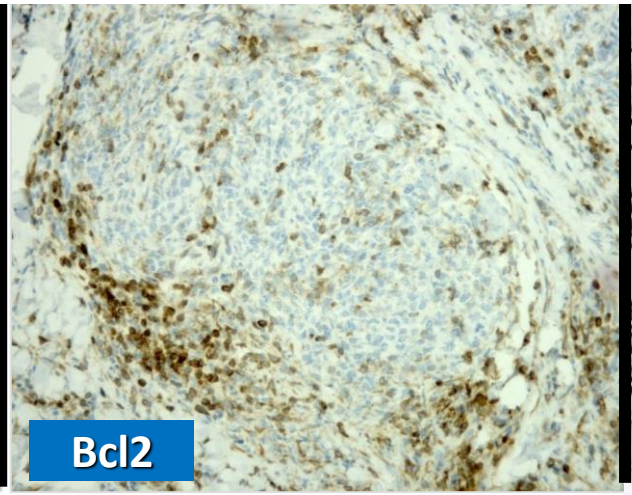
Dysbalance κ/λ (75% cases)

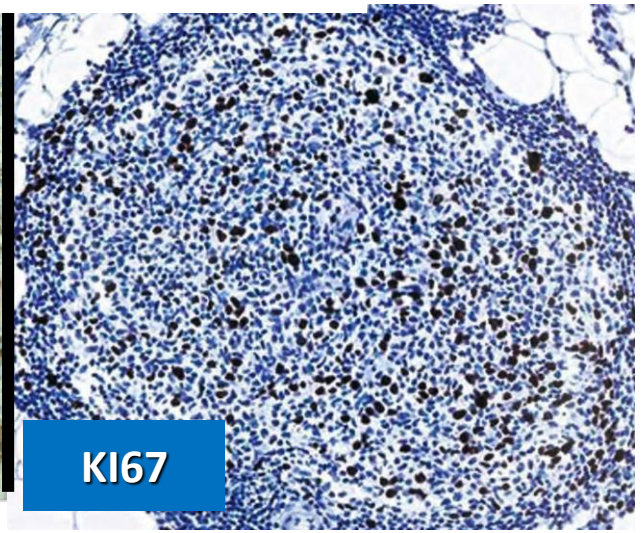


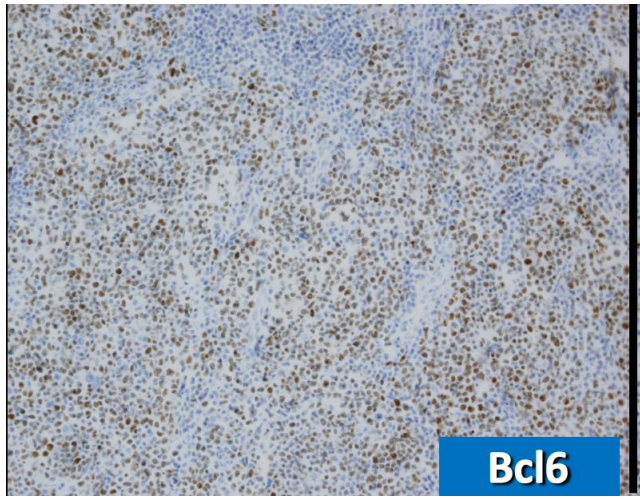


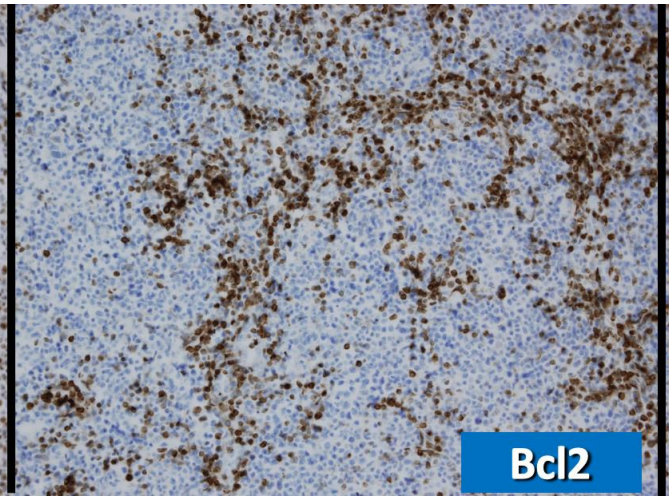
PC Follicular Center Lymphoma

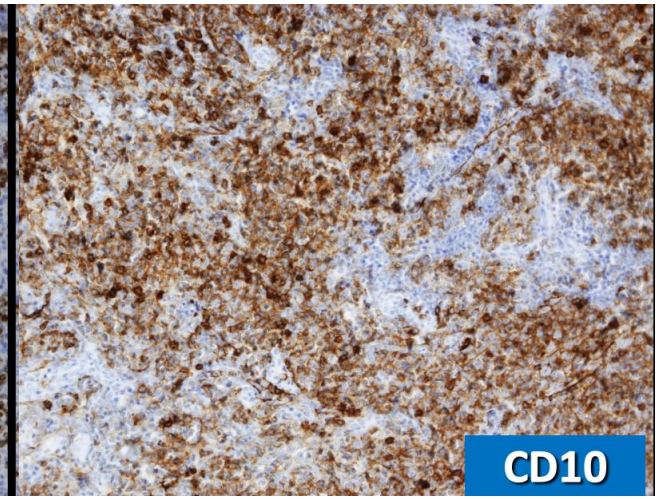




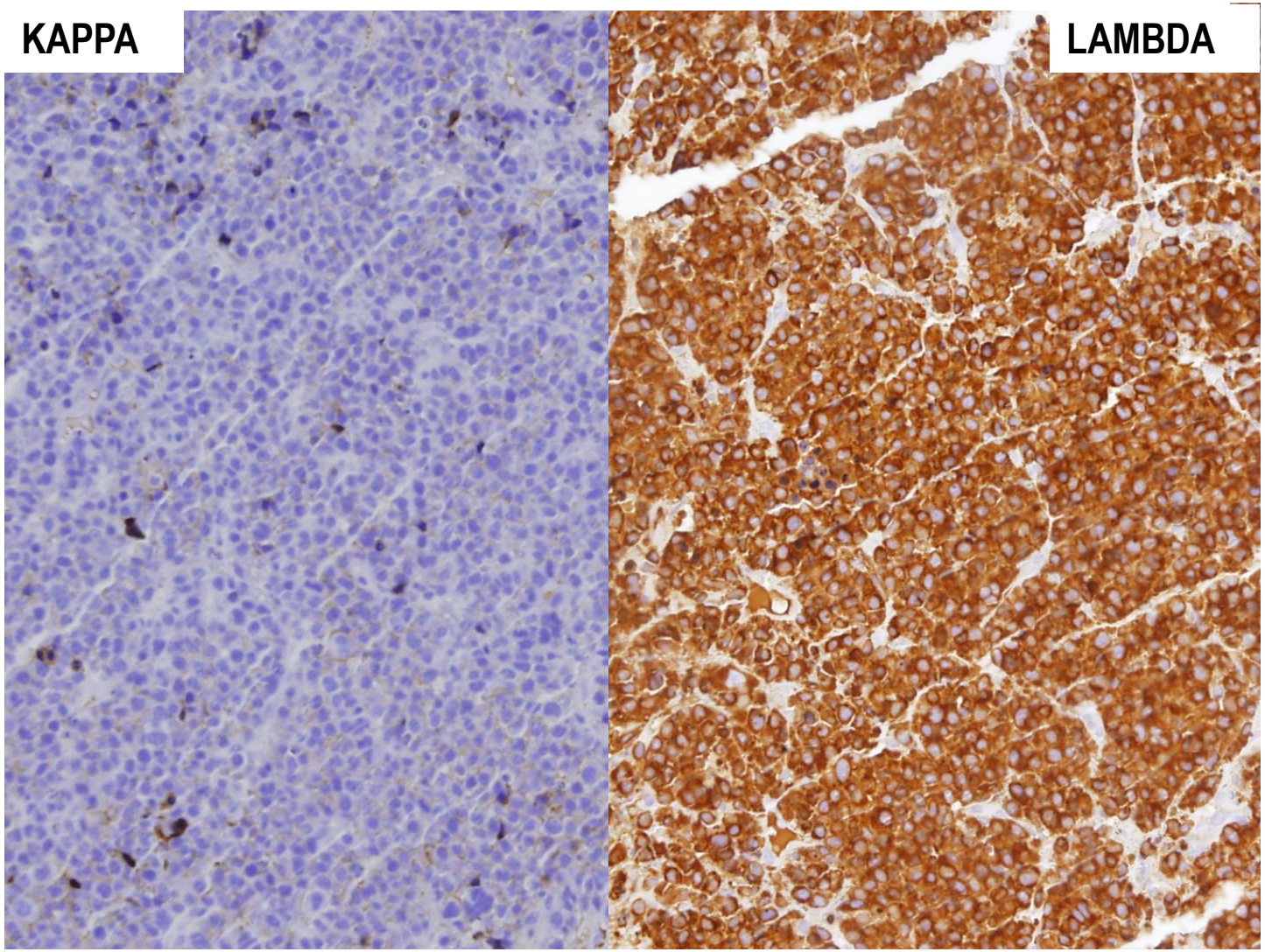








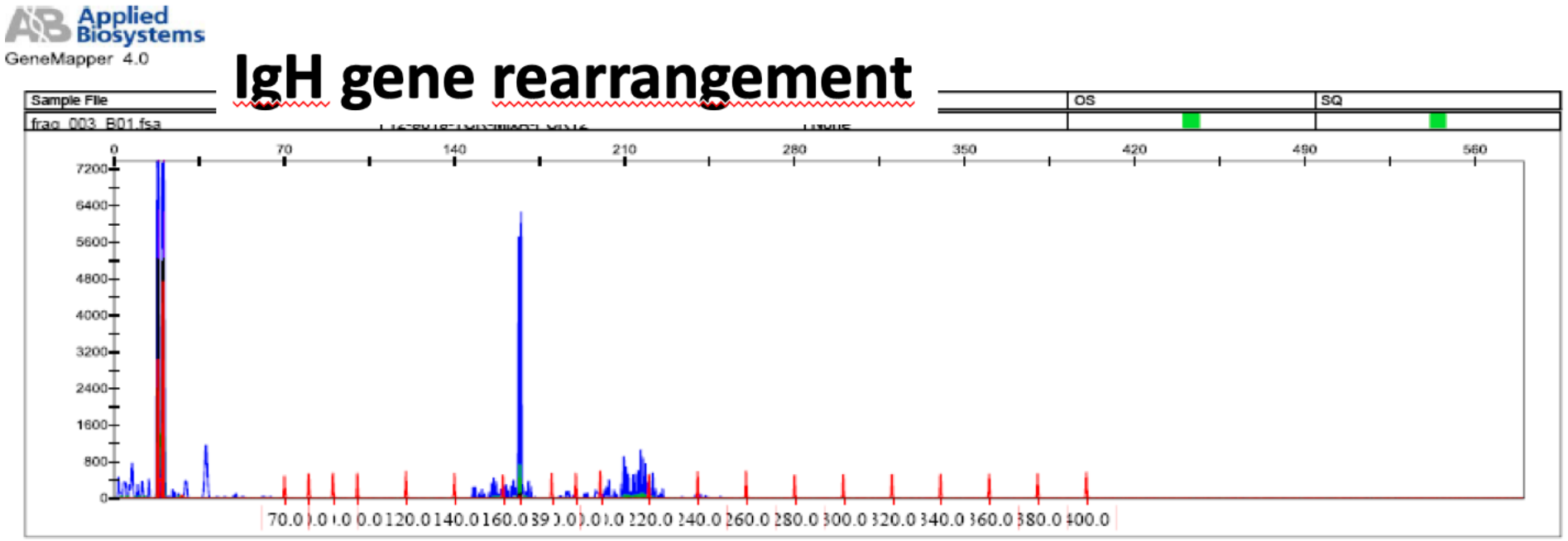
PC Follicular Center Lymphoma



n34

PC Follicular Center Lymphoma

Genetic/molecular (4th pillar)



PC Follicular Center Lymphoma

What to order in PC FCL?

Blood cell count, differential

Blood chemistry (incl. LDH)

Serum electrophoresis

Flow cytometry.

BCR rearrangement peripheral blood

CT/PET-CT

Bone marrow biopsy (11% PCFCL +)

PC Follicular Center Lymphoma

Table 4. Recommendations for initial management of the 3 main types of CBCL

Disease type and extent	First-line therapy	Alternative therapies
PCFCL		
Solitary/localized	Local radiotherapy Excision	IFN-α i.l. Rituximab i.l.
Multifocal	Wait-and-see Local radiotherapy Rituximab i.v.	R-CVP/CHOP‡
Leg lesions	R-CHOP	
Cutaneous relapse	SAME APPROACH	

N Senff. Blood 2008

PC Follicular Center Lymphoma

Cumulative studies	Patients, N	CR, no. (%)	Relapse, no. (%)
PCFCL			
Radiotherapy	460	457/460 (99)	216/457 (47)
Multiagent chemotherapy	104	88/104 (85)	42/83 (51)*
R-CHOP	2	1/2 (50)	0/1 (0)
Interferon-α	7	7/7 (100)	2/7 (29)
Rituximab intralesional	12	10/12 (83)	4/10 (40)
Rituximab intravenous	28	21/28 (75)	4/19 (21)*
Excision	93	91/93 (98)	36/91 (40)
Chemoradiotherapy	7	7/7 (100)	1/7 (14)

N Senff. Blood 2008

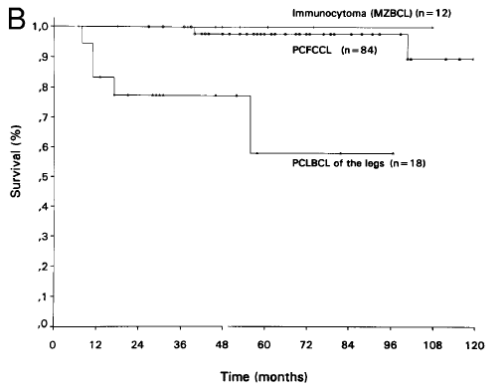
PC Follicular Center Lymphoma

Prognosis

Excellent. 5y. Survival, 95%

Cutaneous relapses 30%

Extracutaneous spread: 5-10%



Do worsens prognosis…

Multiple lesions?	**NO**
High% blast cells?	**NO**
Presence t(14;18)?	**NO, but…**
bcl2 expression?	**NO, but…**
Involvement legs?	**Maybe**

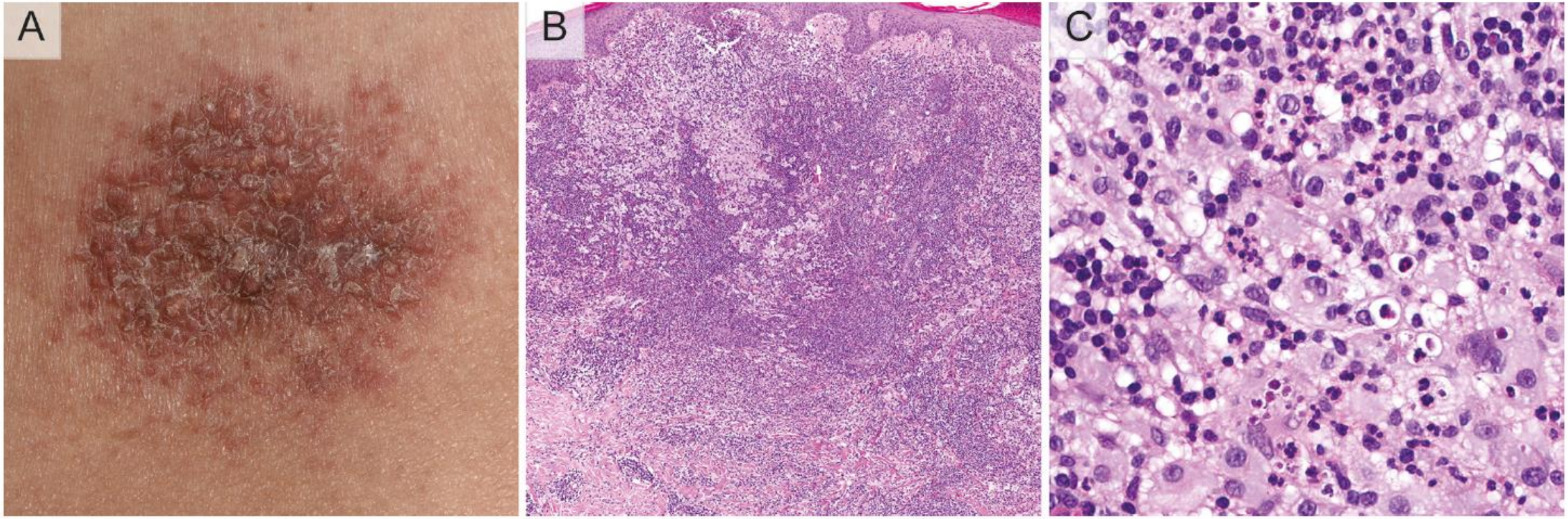
Grange F JCO 2001
Santucci M Cancer 1991
Goodlad JF AmJSurgPatol 2002
Senff N JCO 2007

Primary cutaneous B-cell lymphoma mimickers

Primary cutaneous B-cell lymphoma mimickers

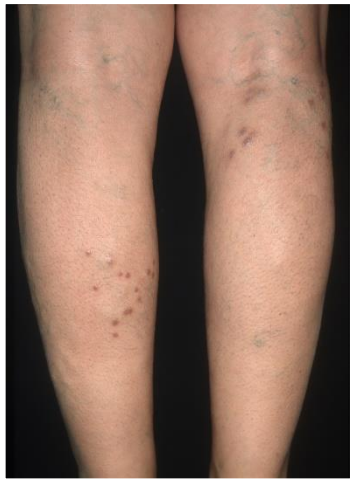
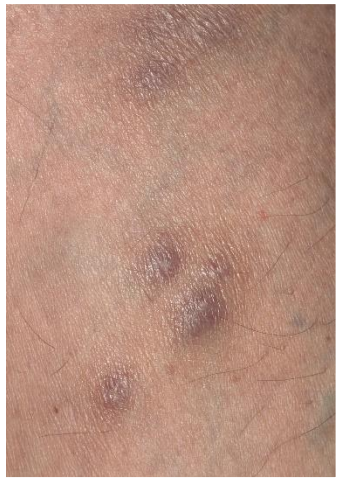
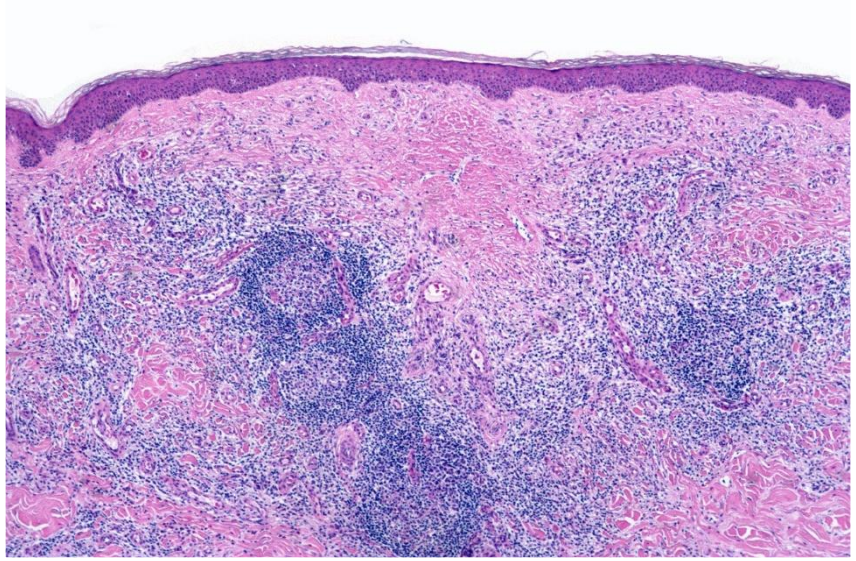
- B-cell psesudolymphoma
- Lymphocytoma cutis
  - Reactive
  - *B. burgdorferi,* insect bites, drugs, vaccinations, acupuncture, pierced, medicinal leech therapy, tattoos…..
- Cutaneous IgG4-related disease
  - Fibrosis
  - IgG4/IgG>40%
  - >10IgG4+ plasma cells/high-power field
- Lupus erythematosus variants
  - Polyclonal T lymphocytes
  - Clusters of CD123+ plasmacytoid dendritic cells
- Cutaneous Rosai-Dorfman Disease
  - sinus histiocytosis with massive lymphadenopathy
  - Foamy histiocytes
  - CD68+, S100+, CD1a-
  - emperipolesis
- Cutaneous extramedullary hematopoiesis
- Histiocytoid Sweet Syndrom
  - immature myeloid cells
- Cutaneous manifestation of Castelman disease
  - HHV8
- Angiolymphoid hyperplasia with eosinophilia

Cutaneous Rosai-Dorfman Disease



Roenneberg S et al. Acta Derm Venereol. 2018 Jan 12;98(1):165-166.

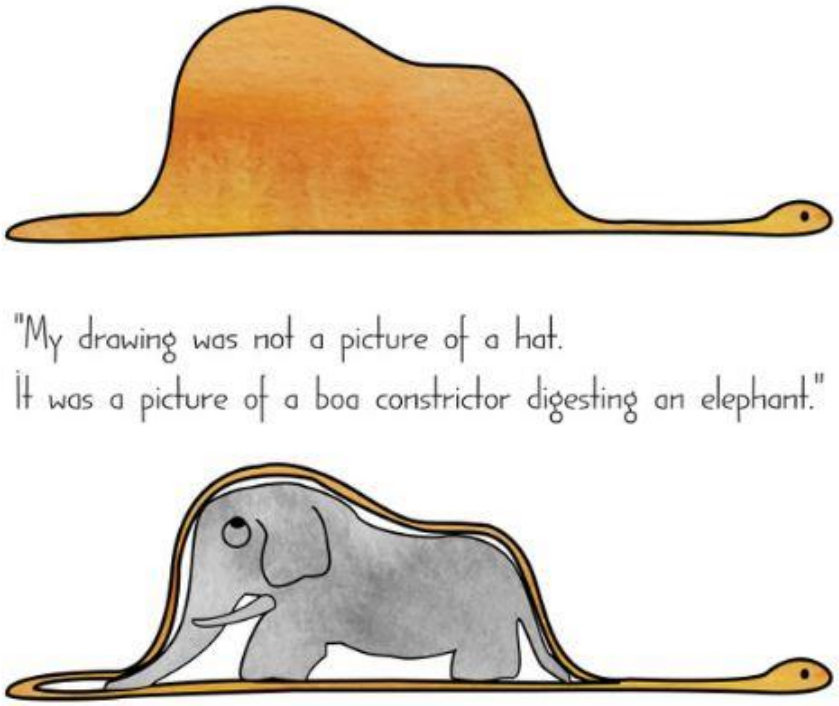
B-cell psesudolymphoma / Lymphocytoma cutis


Smolle, J., et al. (2000). "Multiple pseudolymphomas caused by Hirudo medicinalis therapy." Journal of the American Academy of Dermatology **43**(5): 867-869.

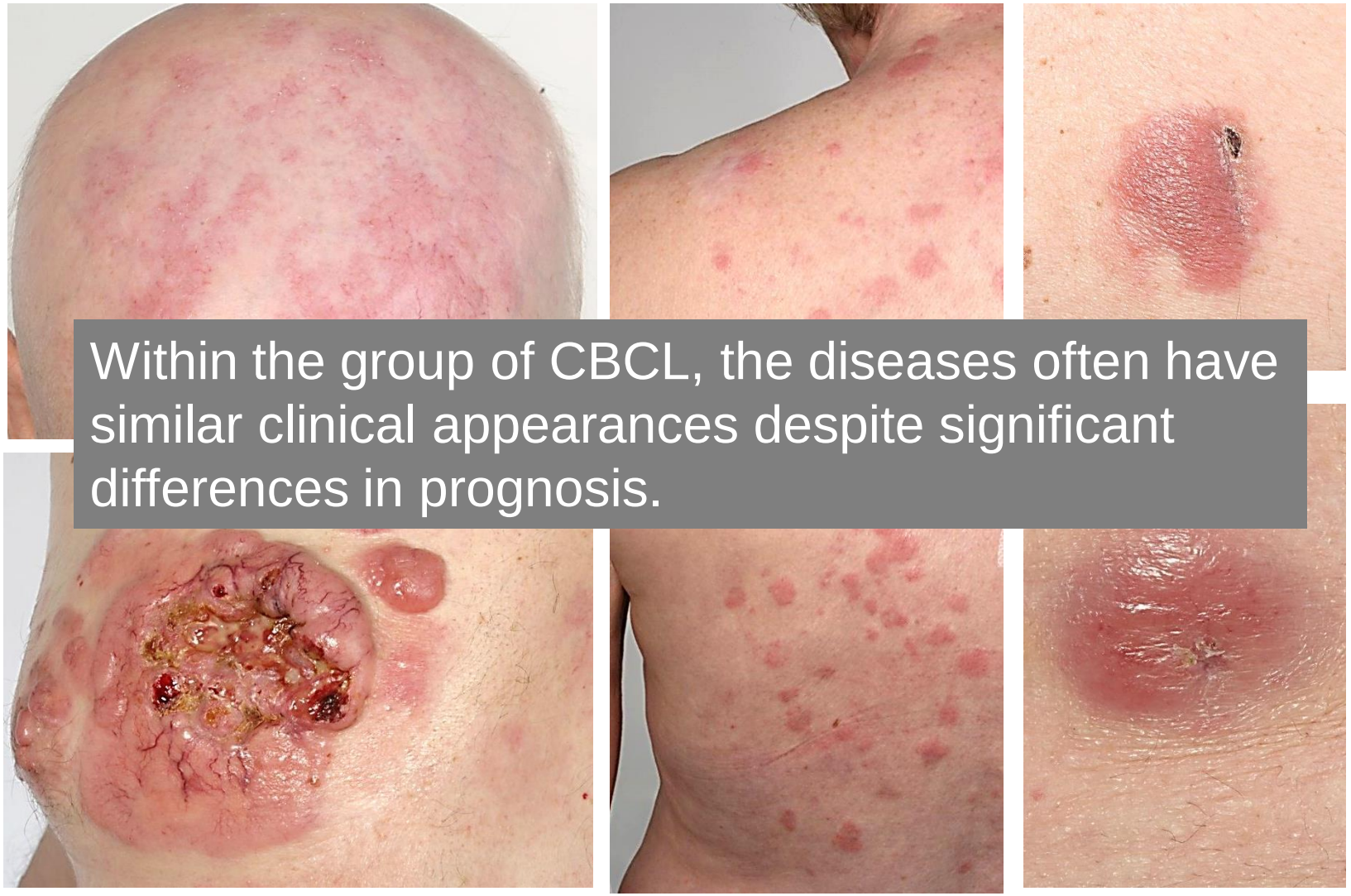
Take-home message

1. PCMZL & PCFCL are the two most common primary cutaneous B-cell lymphomas
2. PCMZL & PCFCL have good prognosis
3. Various skin disorders can simulate primary cutaneous B-cell lymphoma



Antoine de Saint-Exupéry *Le Petit Prince*

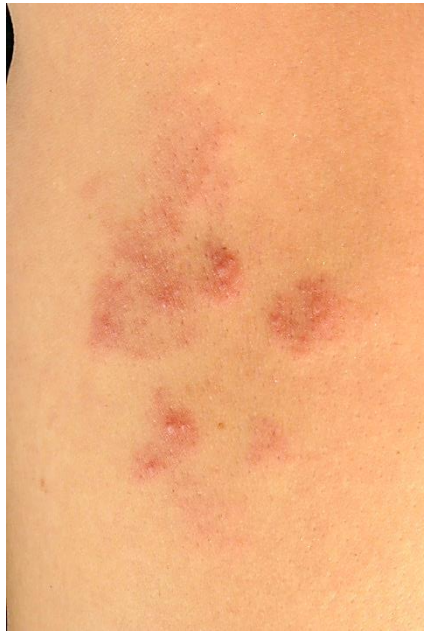
Discussion



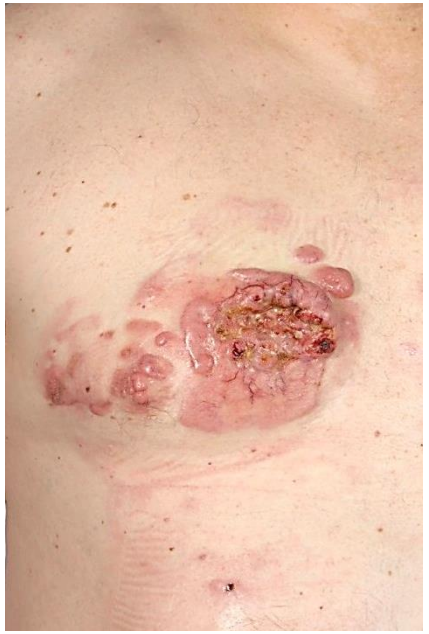
Within the group of CBCL, the diseases often have similar clinical appearances despite significant differences in prognosis.

Median age and anatomical distribution of CBCL[1]

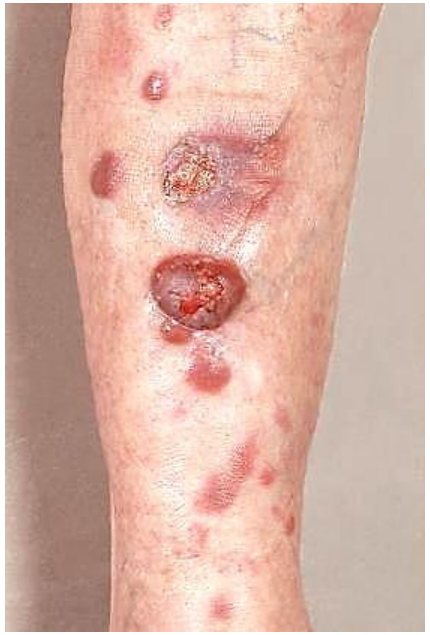
pcMZL 39 y



pcFCL 59 y



pcDLBCL 78 y

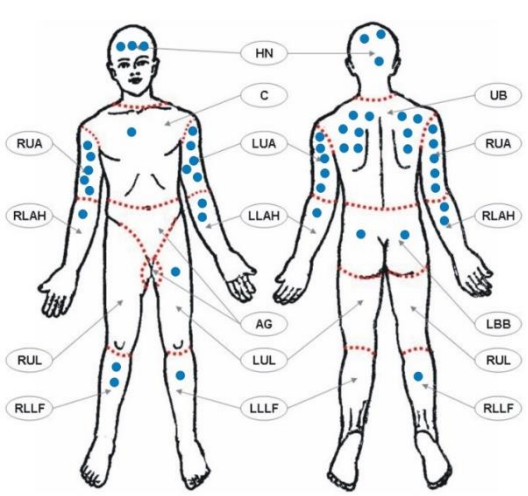
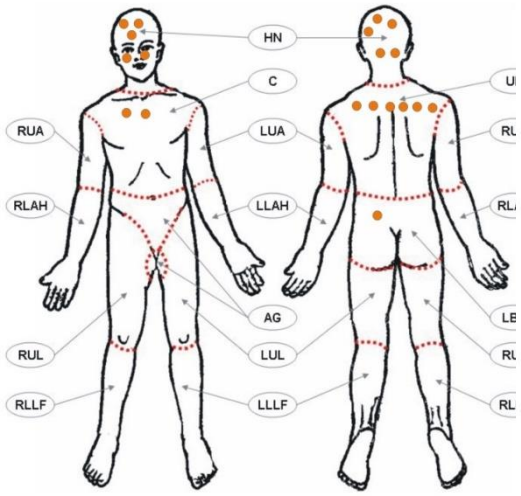
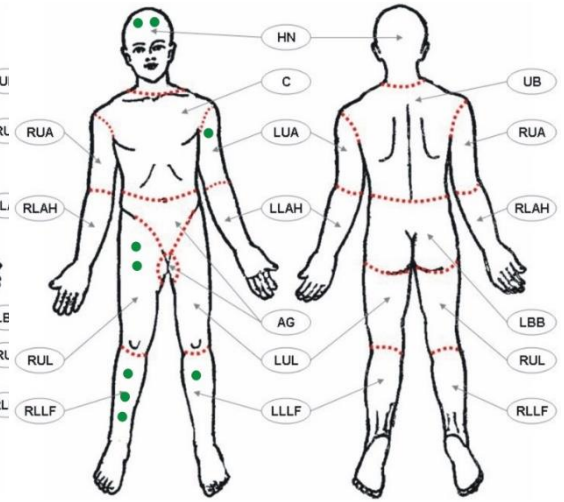


Indolent CBCL

Leg type CBCL

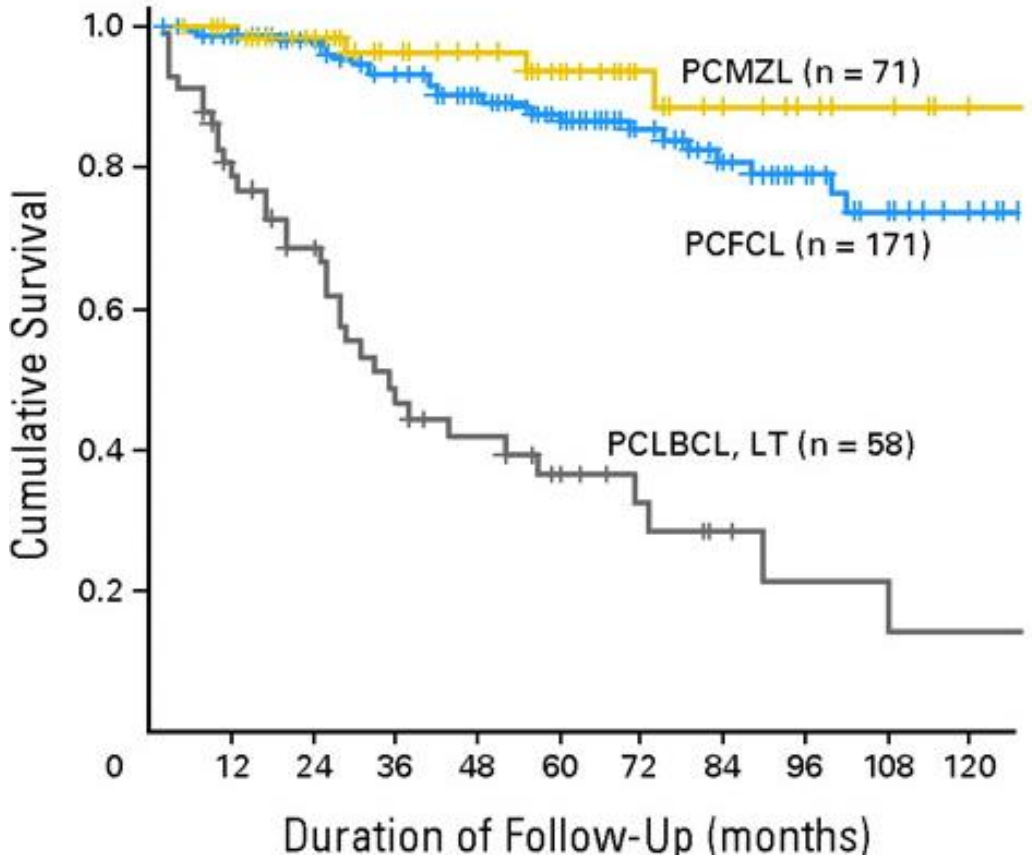
1. Golling, P., et al. (2008). Leuk Lymphoma **49**(6): 1094-1103

CBCL: T stage and anatomical distribution of cutaneous lesions in 54 patients[1]

Marginal zone	Follicle center	Diffuse large cell
		
T1: 39 % T2: 35 % T3: 26 %	63 % 37 % 0 %	43 % 57 % 0 %

1. Golling, P., et al. (2008). Leuk Lymphoma **49**(6): 1094-1103

Overall survival of primary cutaneous B-cell lymphoma[1]



1. Senff, N. J., et al. (2007). J Clin Oncol **25**(12): 1581-1587.

Paraproteinaemia in Primary Cutaneous Marginal Zone Lymphoma

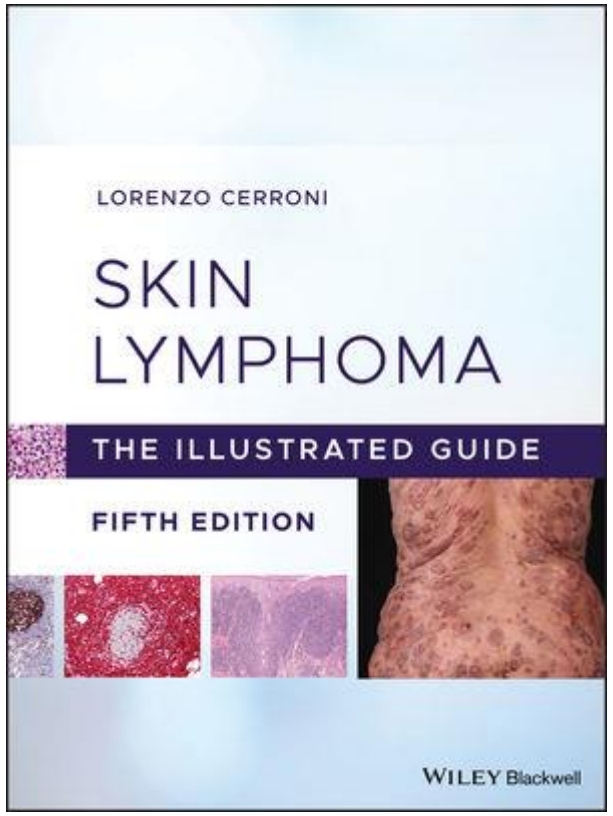
Table I. Detailed overview of tissue light and heavy chain restriction in relation to serological paraproteinaemia

	Tissue		Serum		
Pat. ID	Heavy chain	Light chain	Heavy chain	Light chain	Correlation
A	IgM	Kappa	IgM	None	✓/×
B	Not available	No predom.	IgG	No predom.	×/✓
C	IgM	Lambda	IgG, IgM	Lambda	✓/✓
D	IgA	Kappa	IgM	None	×/×
E	IgA	Kappa	IgA, IgG	Kappa	✓/✓
F	IgM	Kappa	IgM	Kappa	✓/✓
G	No predom.	No predom.	IgA	Kappa	×/×
H	IgM	Kappa	IgM	Kappa	✓/✓
I	IgG	Kappa	IgA	Kappa	×/✓

Predom.: predominance.

Verena G et al. Acta Derm Venereol . 2018 Nov 5;98(10):956-962.

- conventional variant
  - 80% of all cases
- lymphoplasmacytic variant
  - 10% of all cases
  - formerly immunocytoma
  - maybe associated with *B. burgdorferi*
- plasmacytic variant
  - 3% of all cases
  - formerly plasmocytoma
- blastoid variant
  - 2% of all cases
- cutaneous amyloidoma



1. Cerroni L. Skin Lymphoma: The Illustrated Guide, 5th Edition ISBN: 978-1-119-48590-2, 2020 Wiley-Blackwell (Print Book)