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Cutaneous B-cell Lymphomas

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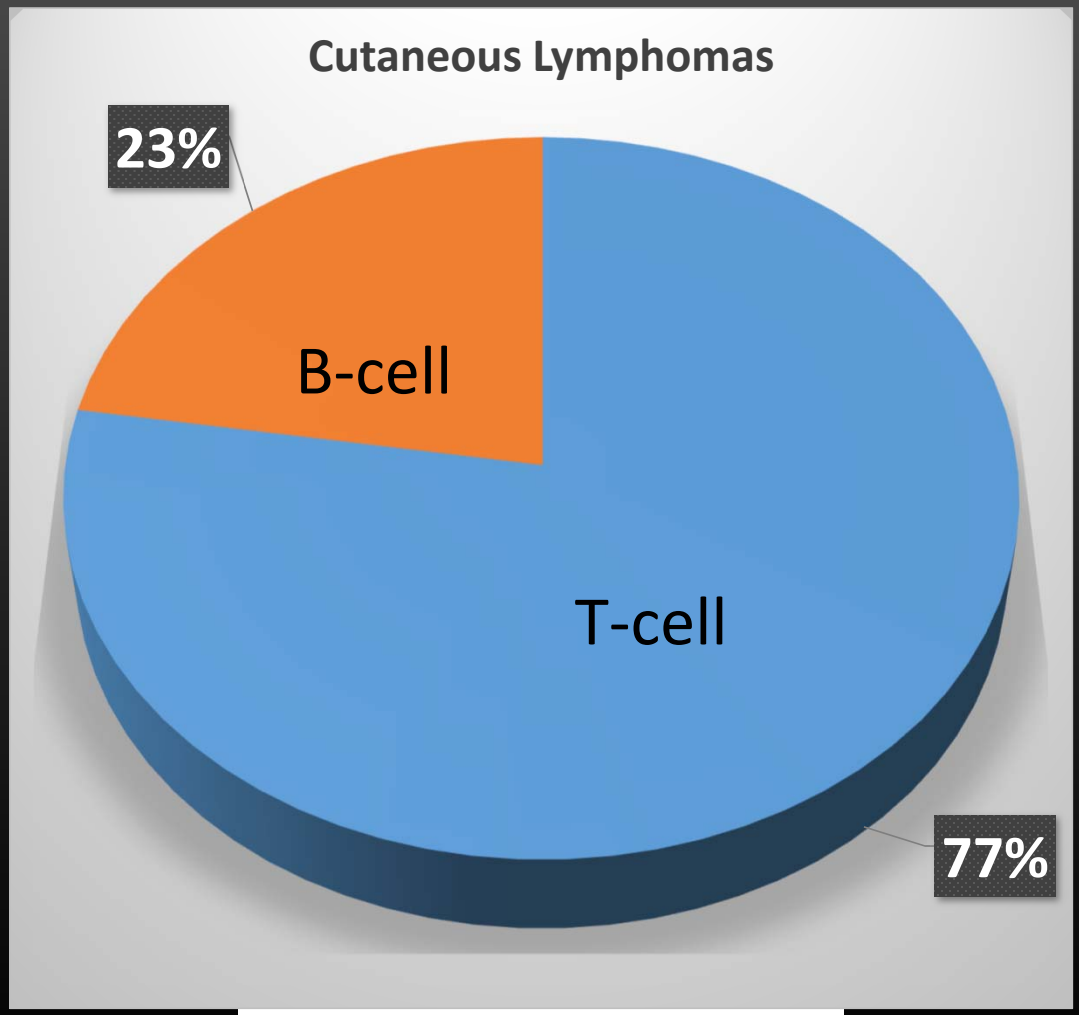
Disclosures

I do not have any significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s) that will be discussed in my presentation

Cutaneous B-cell Lymphomas

- According to the classification of cutaneous lymphomas proposed by the European Organization for Research and Treatment of Cancer (EORTC) and the World Health Organization (WHO) there are three main entities listed under cutaneous B-cell lymphomas:
  - Cutaneous Follicle Center B-cell Lymphoma
  - Cutaneous Marginal Zone B-cell Lymphoma
  - Cutaneous Diffuse Large B-cell Lymphoma, Leg Type



BLOOD, 15 MAY 2005 • VOLUME 105, NUMBER 10

Primary Cutaneous Follicle Center B-cell Lymphoma

Primary Cutaneous Follicle Center B-cell Lymphoma (PCFCL)

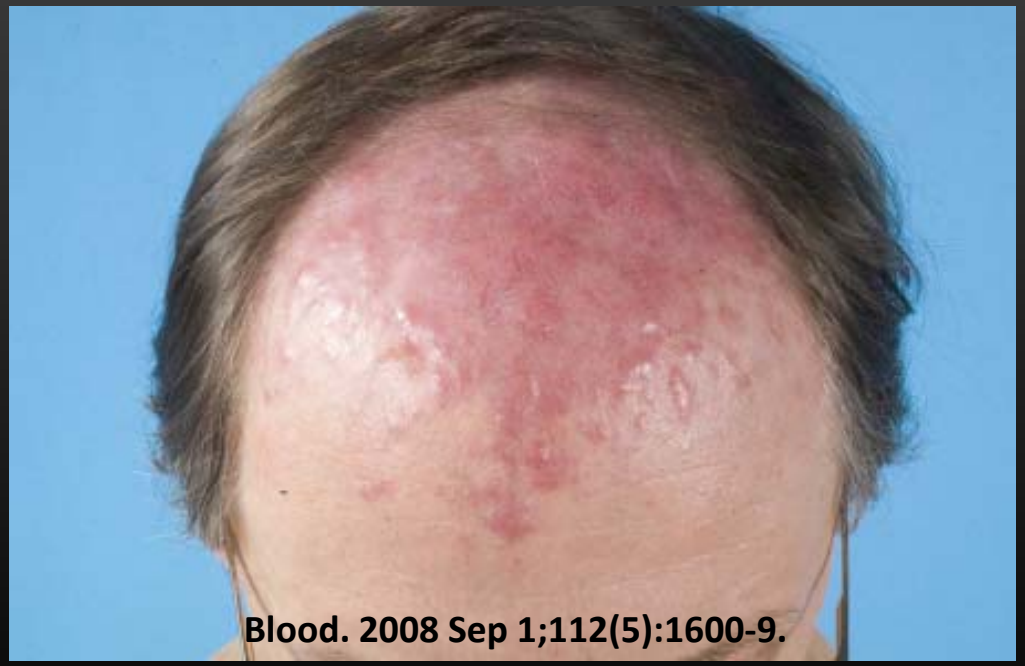
- Neoplastic proliferation of germinal center B-cells confined to the skin
- By definition limited to the skin without evidence of systemic or nodal involvement
- Staging studies are necessary to exclude secondary cutaneous involvement by nodal/systemic follicular lymphoma

Epidemiology and Etiology of PCFCL

- The most common subtype of CBCL (50-60% of CBCL)
- Usually affects 5th to 6th decade of life
- More commonly seen in males
- Etiology is mostly unknown
- *Borrelia burgorferi* DNA has been identified in minority of cases in Europe; but has not been reproducible in non-endemic areas including the United States

Clinical Presentation of PCFCL

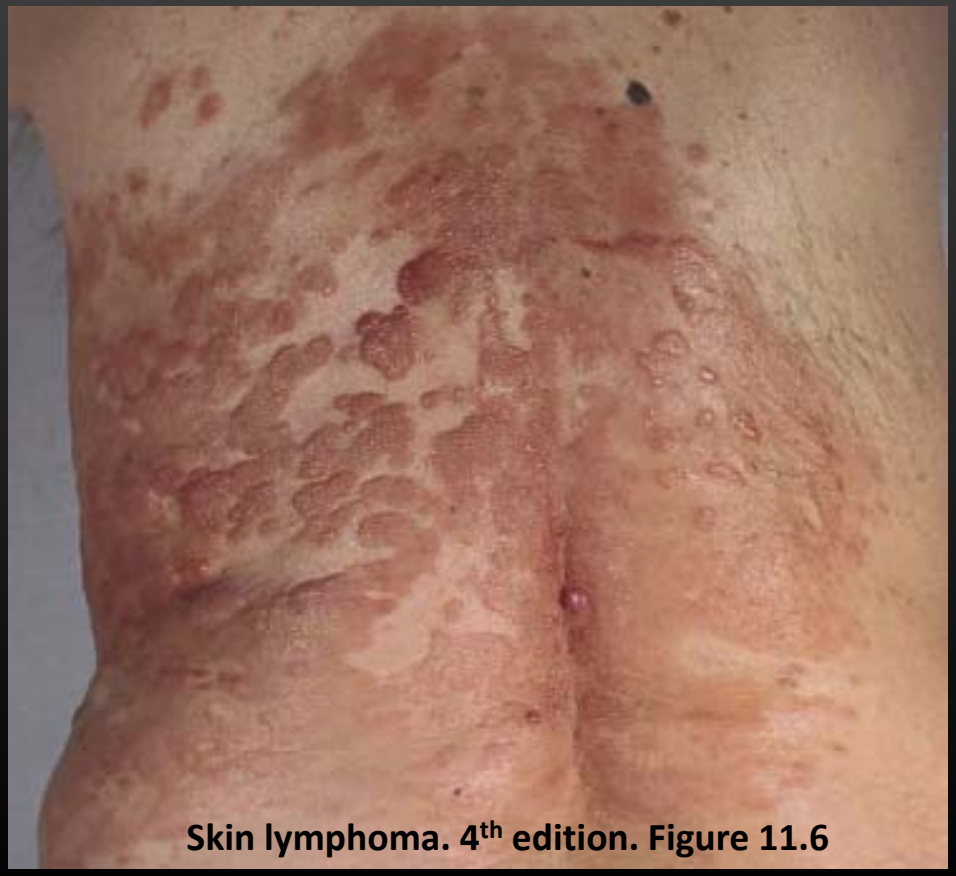
- Firm, non-pruritic, non-painful, non-ulcerated, erythematous papules, plaques, or tumors
- Predilection for the head, neck, and trunk
- Usually clustering as a single lesion, rarely can be multifocal



Blood. 2008 Sep 1;112(5):1600-9.

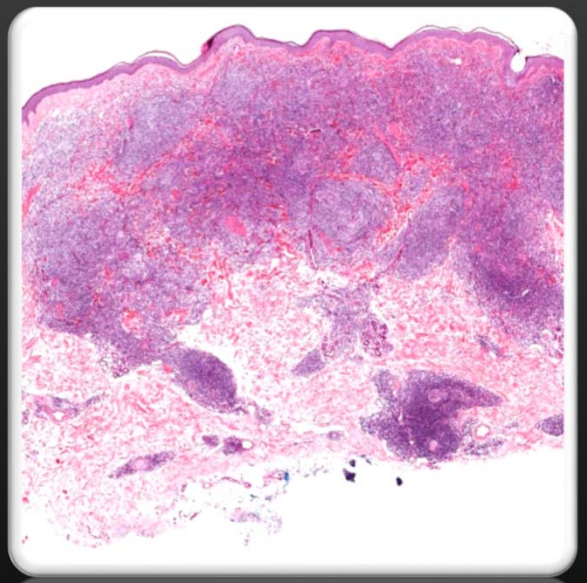
Clinical Presentation of PCFCL

- Can sometimes be larger with surrounding figurate erythema mostly on the trunk and extremities also known as “Crosti’s Lymphoma”
- Dr. Crosti (1951) reported seven patients with what was reported back then as reticulohistiocytoma of the dorsum
- These are now recognized to represent PCFCL

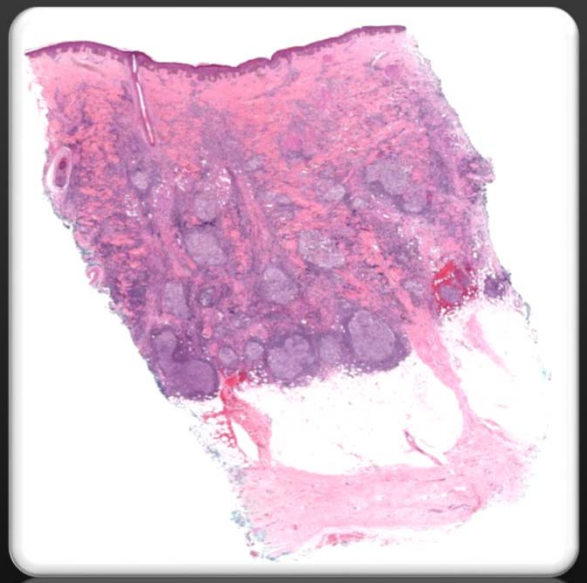


Skin lymphoma. 4th edition. Figure 11.6

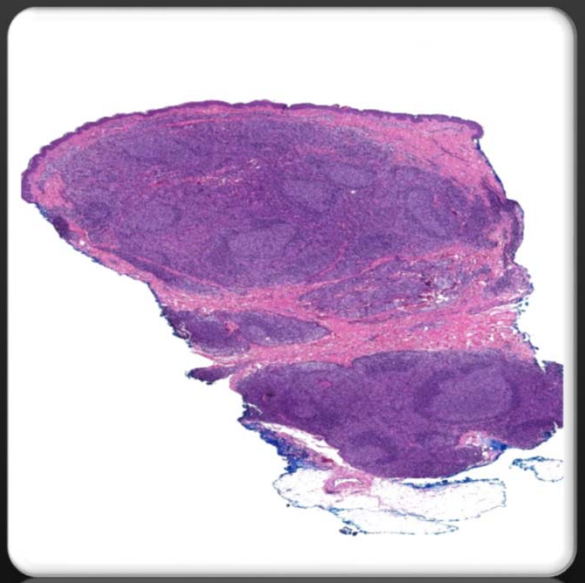
Histopathology of PCFCL



Diffuse pattern



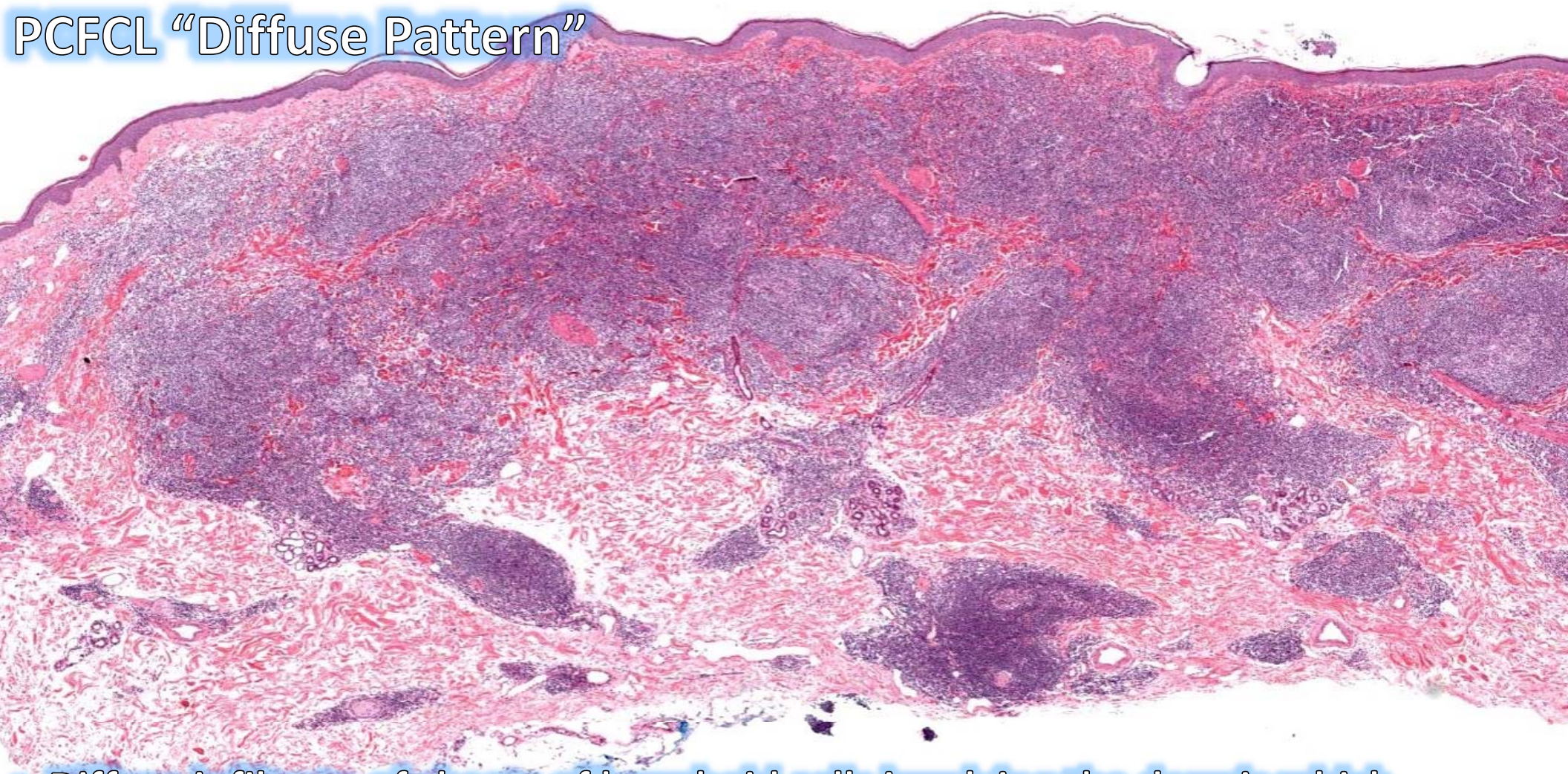
Follicular pattern



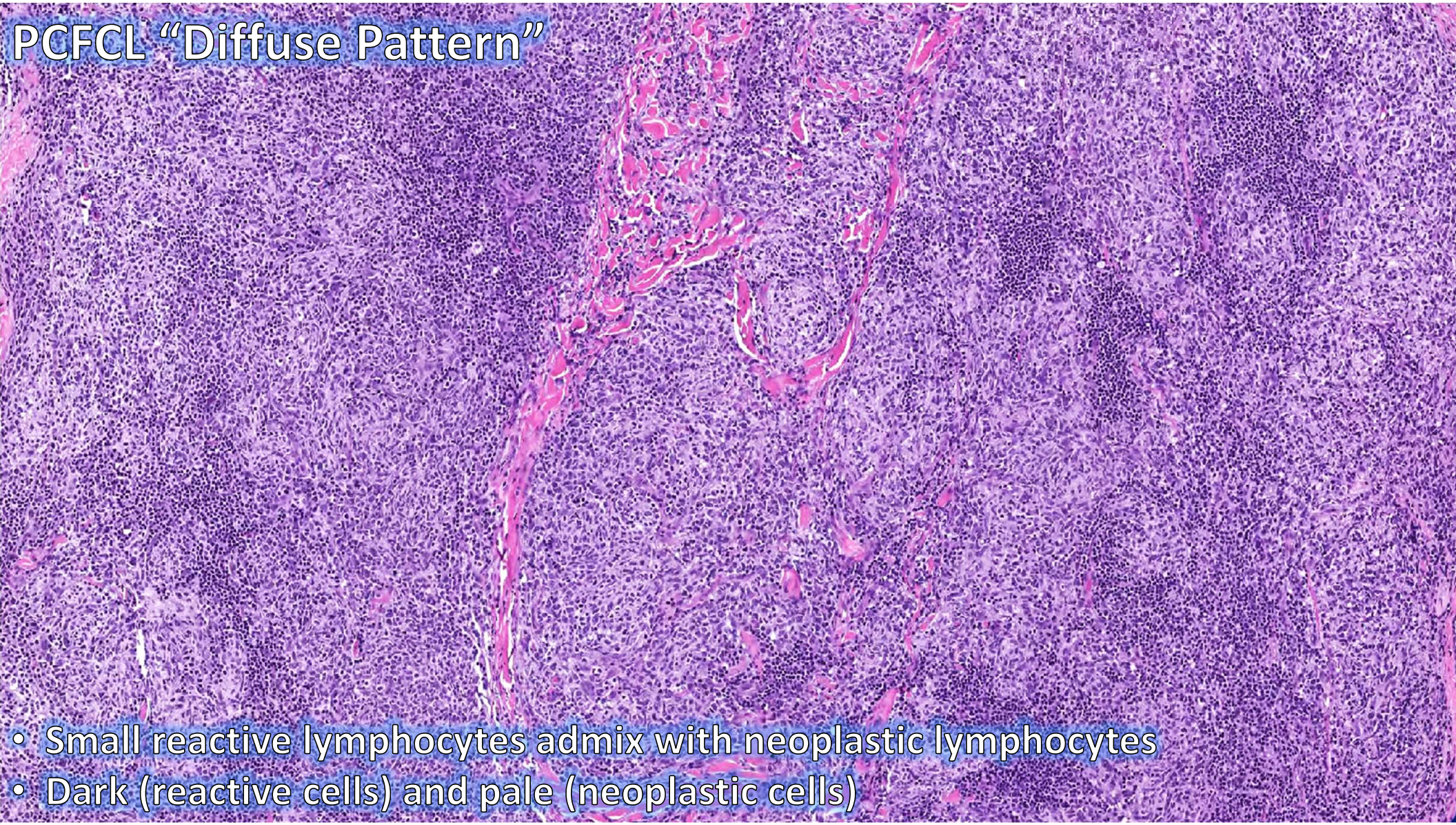
Mixed patterns

* Follicular architecture is not a prerequisite for diagnosis (unlike nodal counterpart)

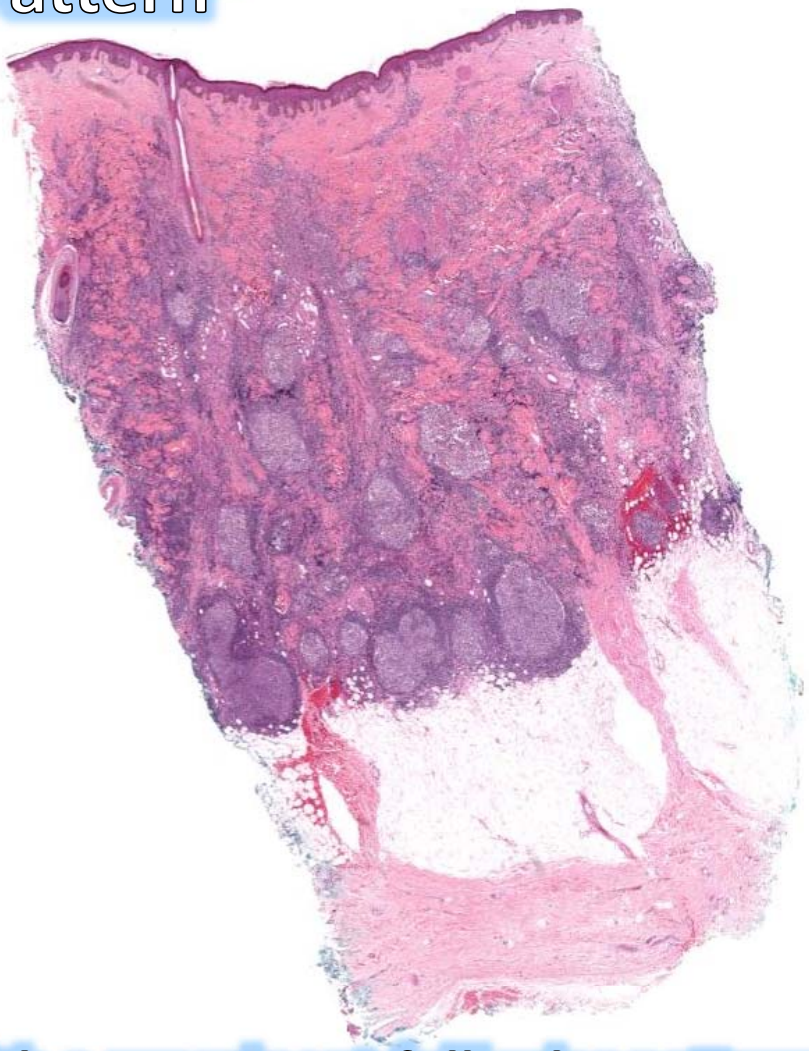
PCFCL “Diffuse Pattern”



- Diffuse infiltrate of sheets of lymphoid cells involving the dermis which commonly extends into the subcutaneous fat

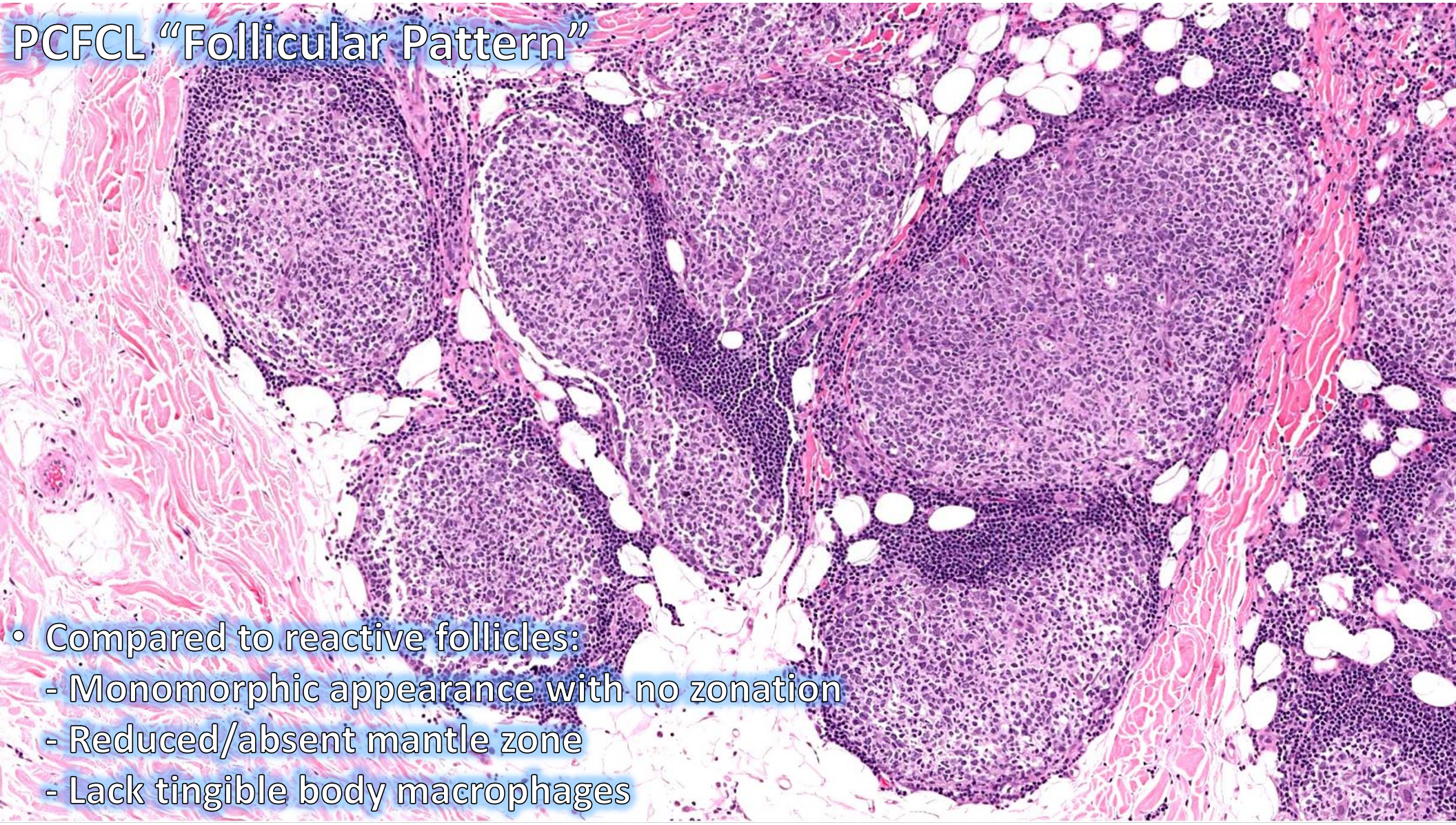

PCFCL “Diffuse Pattern”
• Small reactive lymphocytes admix with neoplastic lymphocytes
• Dark (reactive cells) and pale (neoplastic cells)

PCFCL “Follicular Pattern”

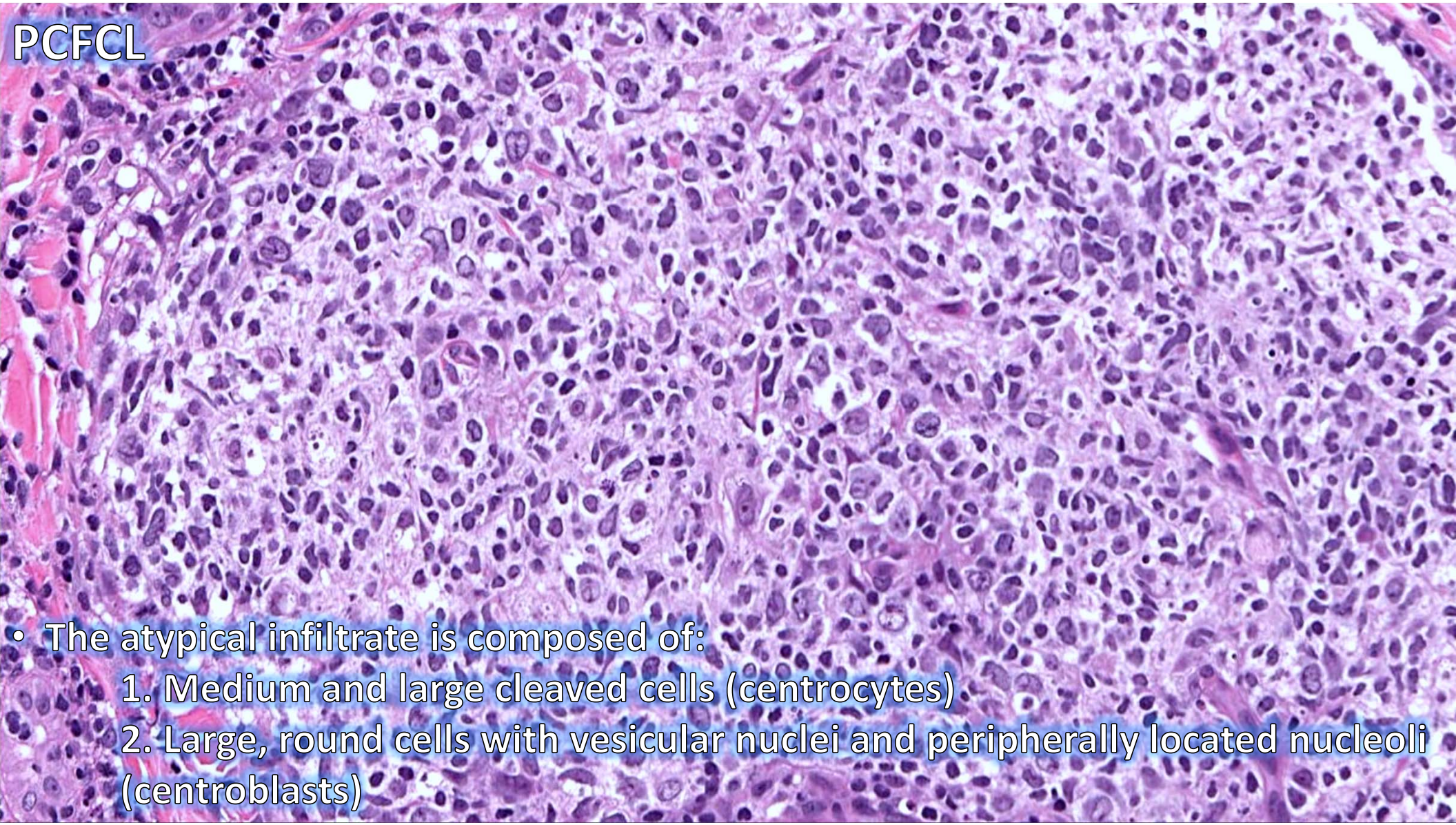


- Nodular infiltrates with a prominent follicular pattern

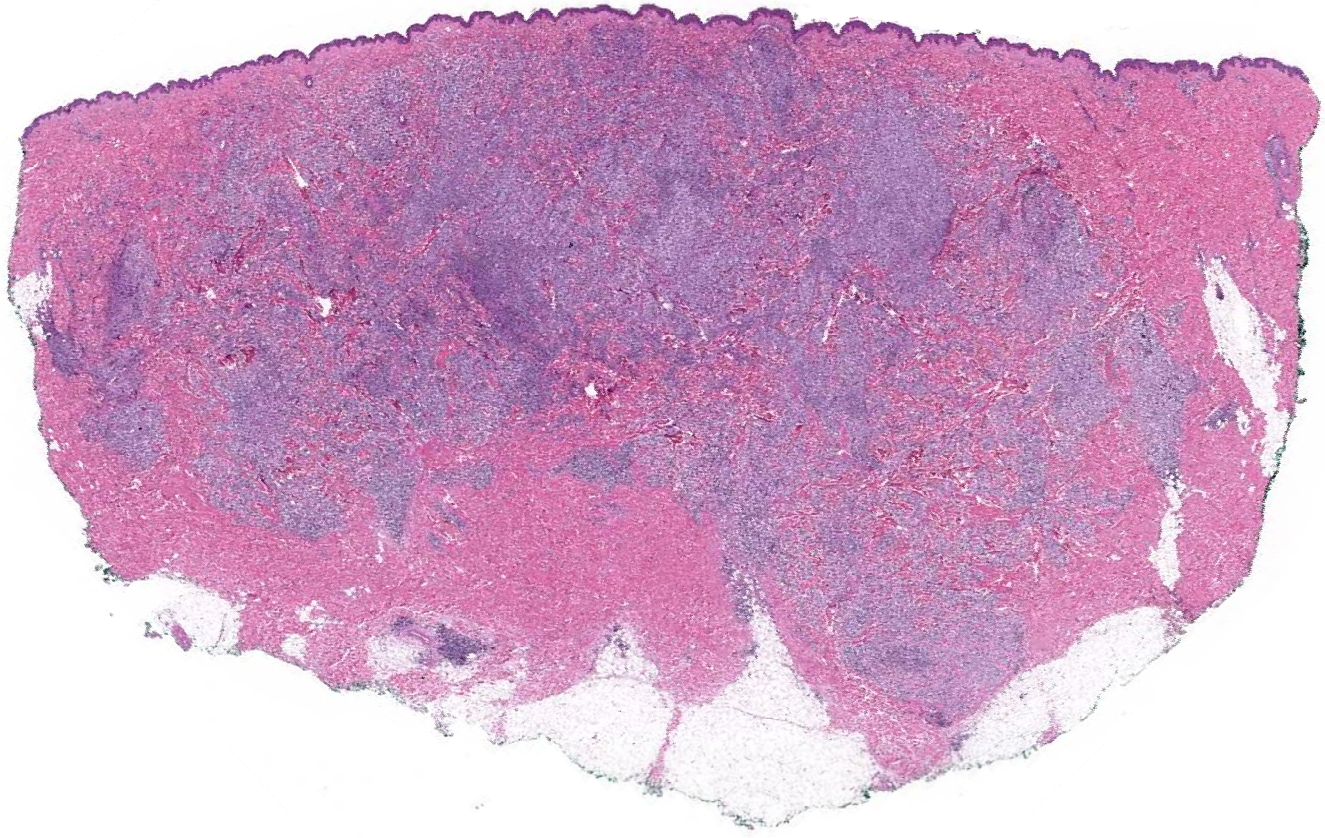
PCFCL "Follicular Pattern"



- Compared to reactive follicles:
  - Monomorphic appearance with no zonation
  - Reduced/absent mantle zone
  - Lack tingible body macrophages

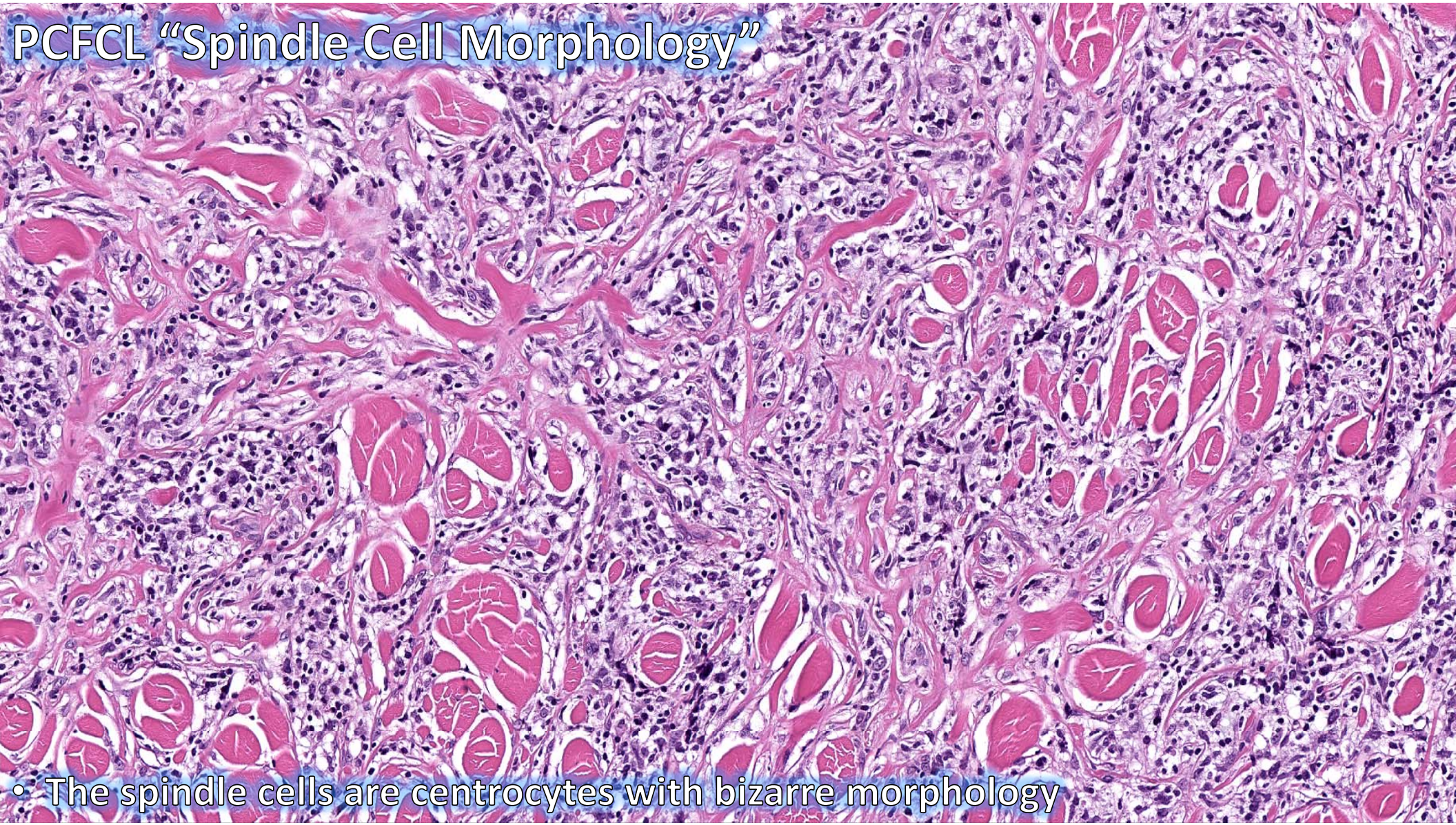

PCFCL
• The atypical infiltrate is composed of:
1. Medium and large cleaved cells (centrocytes)
2. Large, round cells with vesicular nuclei and peripherally located nucleoli (centroblasts)

PCFCL “Spindle Cell Morphology”



- Also called “cutaneous spindle cell/sarcomatoid B-cell lymphoma” and was thought to be a variant of Diffuse large B-cell lymphoma

PCFCL “Spindle Cell Morphology”



- The spindle cells are centrocytes with bizarre morphology

Cutaneous Spindle-Cell B-Cell Lymphomas

Most are Neoplasms of Follicular Center Cell Origin

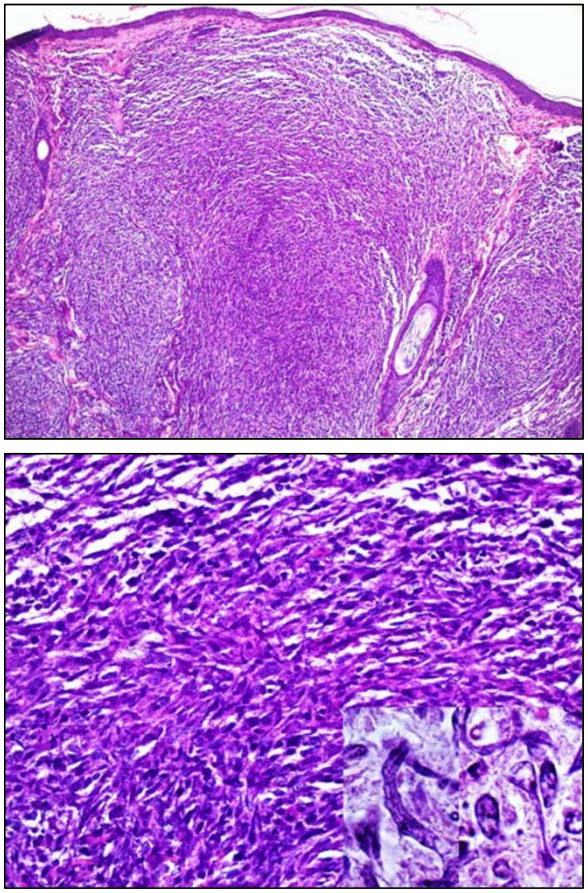
(*Am J Surg Pathol* 2015;39:737–743)

TABLE 1. Clinical and Immunohistochemical Features of cSCBCLs in the Current Study

Case	Sex, Age (y)	Location	% SC	CD20/PAX5*	Bcl-6	CD21	CD10	Bcl-2	MUM-1	CD30	PD-1	Diagnosis
1	F, 71	Knee	3	++	+	–	–	++	+	–	ND	SC FCBCL
2	M, 65	Scalp	2	++	–	++	–	+	–	–	ND	SC FCBCL
3	M, 77	Nose	3	++	–	–	–	+	+	–	ND	SC DLBCL-other
4	M, 85	Scalp	1	++	++	++	–	++	–	+	–	SC FCBCL
5	M, 38	Head	3	++	++	++	–	++	–	–	–	SC FCBCL
6	F, 45	Back	2	++	++	–	++	++	–	–	–	SC FCBCL
7	M, 44	Scalp	3	++	++	++	–	–	–	–	–	SC FCBCL
8	M, 84	Leg	4	++	++	–	–	++	++	–	ND	SC DLBCL-leg type
9	M, 82	Thigh	4	++	+	–	–	++	–/+	–	ND	SC FCBCL
10	M, 58	Scalp	1	++	++	++	++	++	–/+	–	–/+	SC FCBCL
11	M, 33	Head	2	++	++	++	–	–	–/+	–	–/+	SC FCBCL
12	M, 27	Cheek	3	++*	++	++	TE/ND	TE/ND	TE	++	ND	SC FCBCL
13	M, 44	Scalp	3	++/++*	++	–	ND	–	ND	–	ND	SC FCBCL
14	M, 34	Buttocks	1	++	++	++	ND	–	–	–/+	ND	SC FCBCL
15	M, 43	Back	3-4	++	++	ND	–	++	–	–	–/+	SC FCBCL
16	F, 50	Back	2-3	++	++	++	–	–	–	–	–	SC FCBCL
17	M, 43	Back	2	++	++	++	+	+	+	–	–	SC FCBCL
18	F, 45	Scalp	1	++	++	ND	–	–	–	–	–	SC FCBCL
19	M, 67	Trunk	2	++	++	ND	ND	++	–	–	–	SC FCBCL
20	M, 60	Back	2-3	++	++	–	–/+	–/+	–	++	–	SC FCBCL
21	M, 48	Scalp	2	++	++	–	–	ND	–	–/+	–	SC FCBCL
22	F, 59	Back	3-4	++	++	–	–	–	–	–/+	–	SC FCBCL
23	F, 59	Back	2	++	++	–	–	–	–	+	–	SC FCBCL
24	M, 69	Chin	1-2	++	++	–	–	–	–	–	–	SC FCBCL

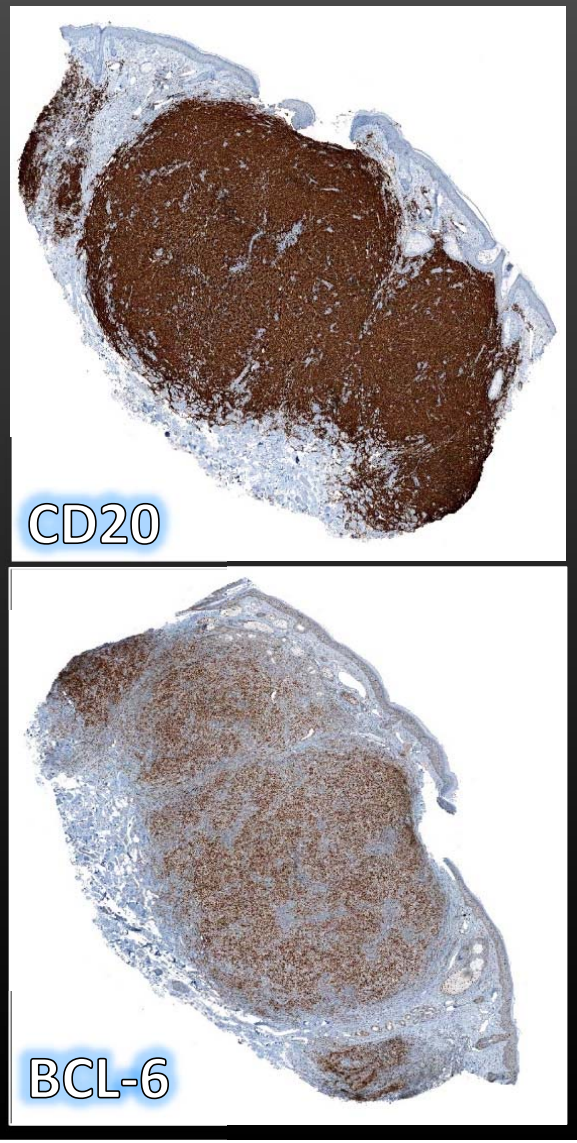
*CD20 or PAX-5 staining.

% SC indicates percentage of spindle cells (1 = 15% to 25%, 2 = 26% to 50%, 3 = 51% to 75%, and 4 = > 75%); –, no labeling; –/+, <1/3; +, 1/3 to 2/3; ++ = most neoplastic cells; F, female; M, male; ND, not done; TE, tissue exhausted.



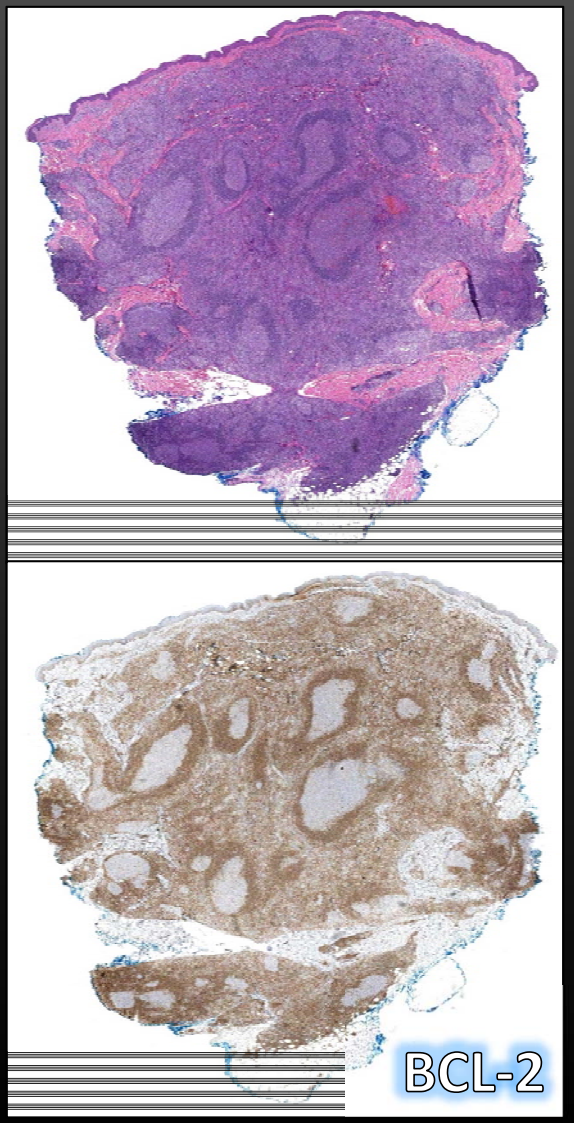
PCFCL Immunohistochemistry

- CD20, CD79a, and PAX5: Positive in the neoplastic B cells
- BCL-6: Positive in the neoplastic cells
- CD10: Mostly positive in the follicular pattern (diffuse pattern tends to be negative)



PCFCL Immunohistochemistry

- BCL-2 expression can be found in minority of cases (10-15%)
- BCL-2 positivity is not synonymous to nodal follicular lymphoma involving the skin



PCFCL Immunohistochemistry

- CD21: Highlights follicular dendritic cells (mainly in follicular pattern)
- Ki-67: Proliferation index usually less than 50% of the neoplastic cells (compared to reactive germinal centers which usually shows ~90% proliferative index)
- MUM-1: Positive only in a minority of cells (<30%)

PCFCL Molecular

- Majority of cases show monoclonal rearrangement of the immunoglobulin heavy chain genes (ranges between 70% - 90%)

- Percentage of cases with t (14;18) is variable in the literature dependent on the country of origin and method used for detection of translocation

Am J Clin Pathol March 2015;143:362-373

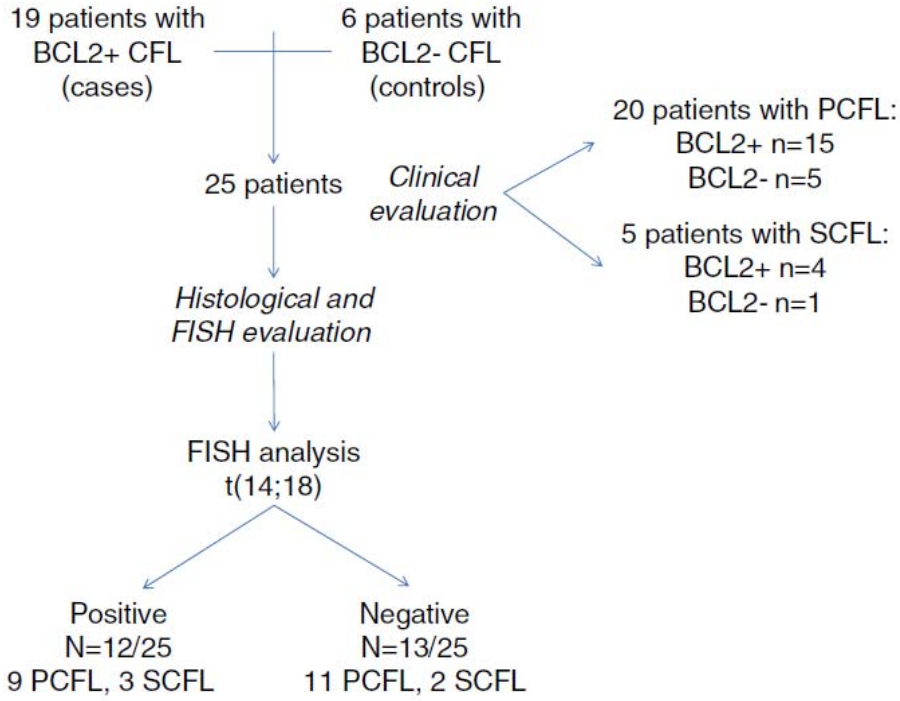
BCL2 Rearrangement (or t(14;18)) Detection by PCR and/or FISH in PCFCL

Author (Year)	No. of Patients	t(14;18) Detection by PCR, No./ Total No. (%)	t(14;18) Detection by FISH, No./ Total No. (%)
Geelen et al (1998)[8]	8	0/8	
Child et al (2001)[9]	5	0/5	
Vergier et al (2004)[7]	30	9/30 (30)	0/17
Aguilera et al (2001)[11]	17	3/17 (18)	
Lawnicki et al (2002)[12]	20	4/20 (20)	
Mirza et al (2002)[13]	32	11/32 (34)	
Kim et al (2005)[14]	13	4/13 (31)	
Streubel et al (2006)[10]	27	0/27	11/27 (41)
Pham-Ledard et al (2015)	47		4/47 (8.5)

Primary Cutaneous Follicle Center Lymphomas Expressing BCL2 Protein Frequently Harbor *BCL2* Gene Break and May Present 1p36 Deletion

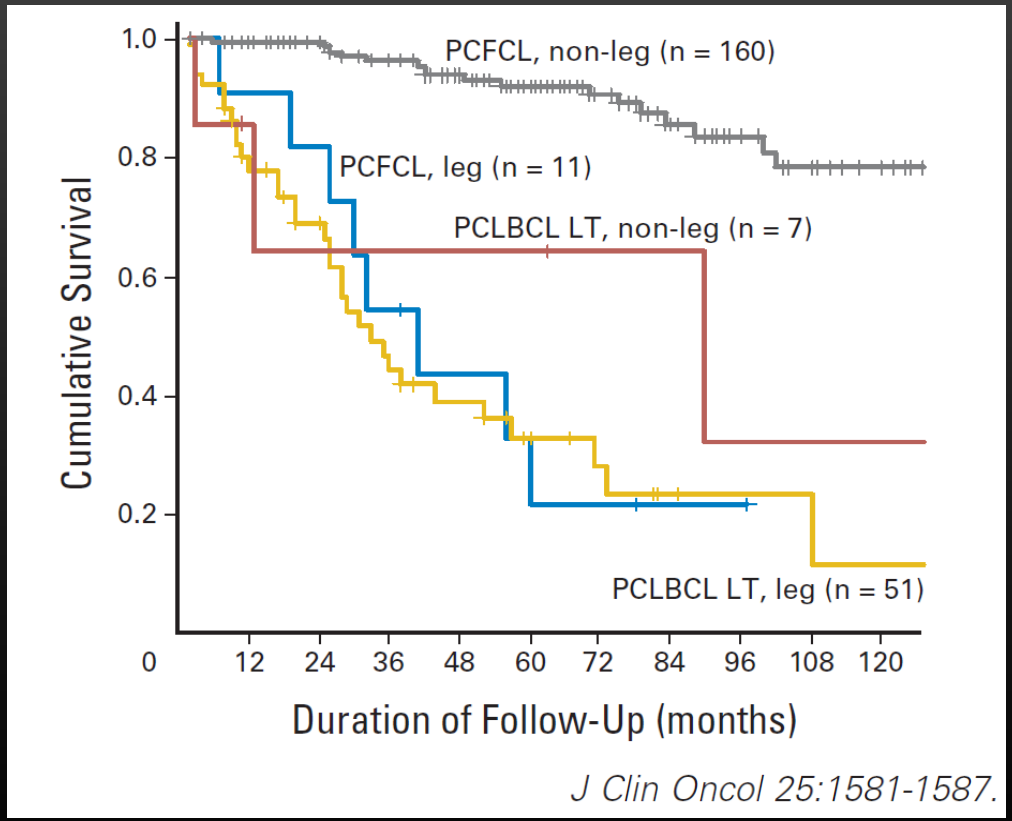
(*Am J Surg Pathol* 2016;40:127–136)

	Phenotype (Positive/Total [%])				Cytogenetics (Positive/Total [%])							
Groups	*BCL6*	*BCL2*	CD23	MUM1	*BCL2* Break	*P*	*IGH/BCL2* Translocation	*BCL6* Break	*IGH* Break	*IGK* Break	*IGL* Break	1p36 Deletion
Total CFL (N = 25)	23/24 (95.8)	19/25 (76)	13/25 (52)	7/20 (35)	12/25 (48)		11/24 (45.8)	2/25 (8)	0/12 (0)	0/12 (0)	0/12 (0)	1/23 (4.3)



PCFCL Prognosis

- The prognosis is very good regardless of the pattern of growth
- They can show local recurrence but rarely spread to extracutaneous sites
- The only exception for the rule is for cases of PCFCL arising on the legs



J Clin Oncol 25:1581-1587.

Primary Cutaneous Marginal Zone B-cell Lymphoma

Primary Cutaneous Marginal Zone B-cell Lymphoma (PCMZL)

- A Low-grade malignant cutaneous B-cell lymphoma characterized by the proliferation of marginal zone cells, lymphoplasmacytoid cells, and plasma cells in the skin

- Previously labeled “primary cutaneous immunocytoma”, “cutaneous plasmacytoma”, and “cutaneous follicular lymphoid hyperplasia with monotypic plasma cells” belong to this group

Epidemiology of PCMZL

- Accounts for 2-7% of all cutaneous lymphomas and 20-40% of all PCBCL
- Usually affects middle aged patients with a median age of 55
- Mostly affects males

Etiology of PCMZL

- Etiology is not completely understood

- Thought to be secondary to chronic antigen stimulation with eventual development of B-cell lymphoma analogous to the extra-nodal MALT-type lymphomas:
  - *Helicobacter pylori* (stomach)
  - *Chlamydiae psittaci* (ocular adnexal MALT lymphomas)
  - *Campylobacter jejuni* (immunoproliferative small intestinal disease)

- A proportion of PCMZL may be related to *Borrelia burgdorferi* infections (mostly in endemic regions in Europe); however, there appears to be no link in other non-endemic regions (United States, Asia)

Clinical Presentation of PCMZL

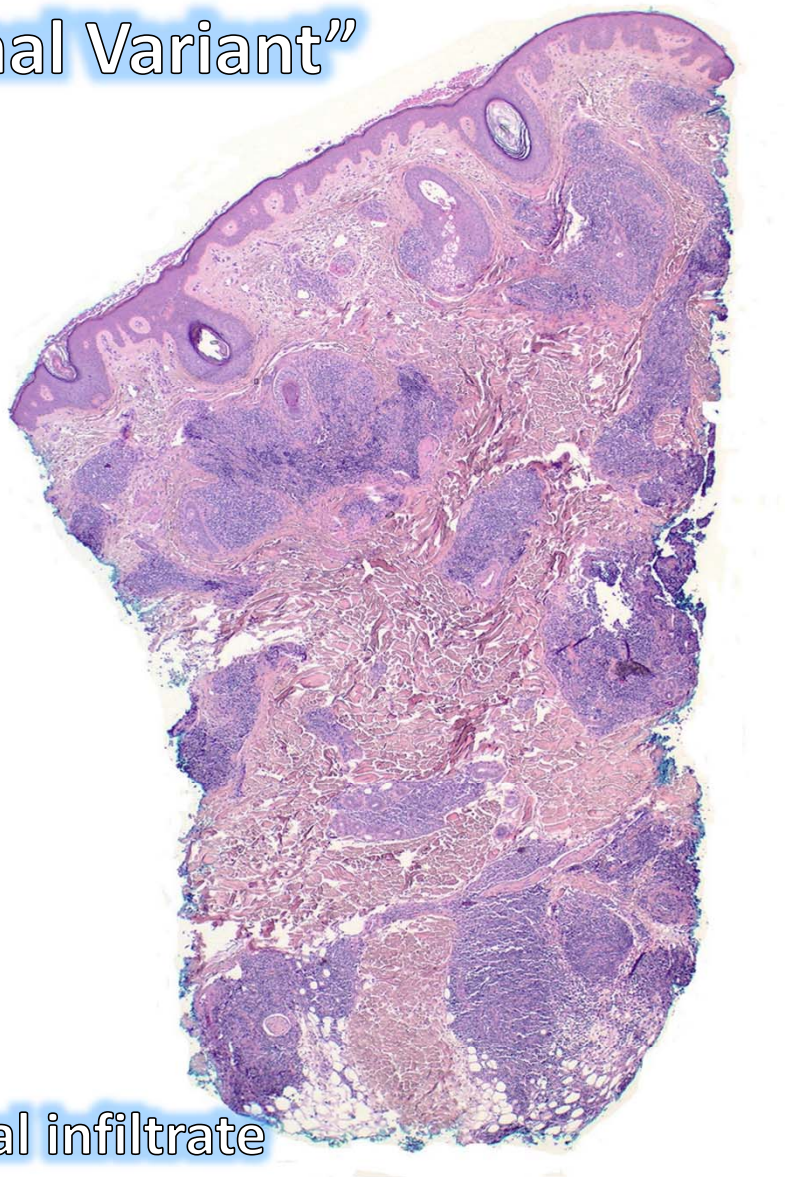
- Solitary lesions or clusters of asymptomatic, reddish papules, nodules and/or plaques
- The trunk (particularly the back) and arms are predominantly affected
- Can affect multiple anatomical sites simultaneously

Skin lymphoma. Figure 12.1-2

Histopathology of PCMZL

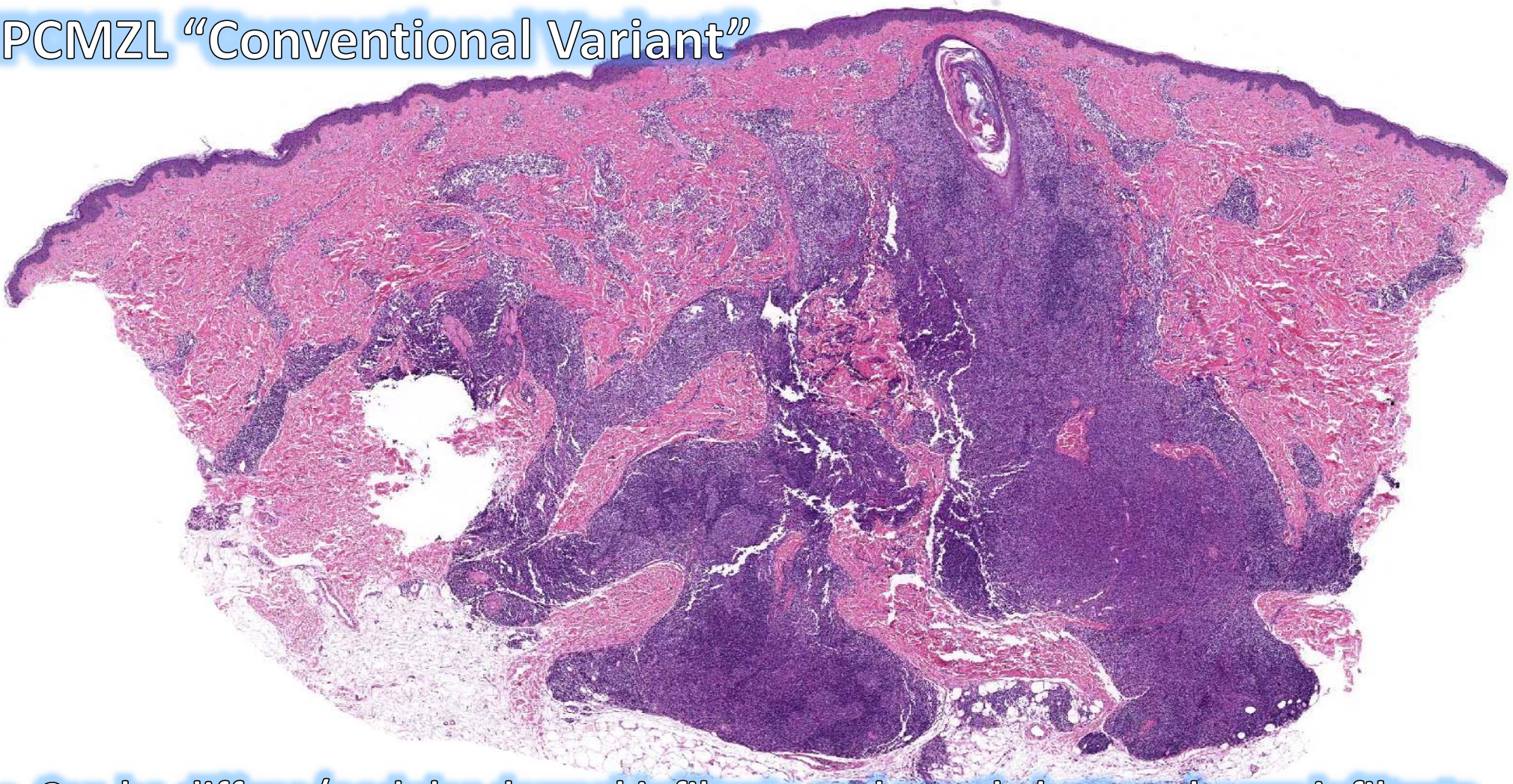
- There are four main histologic variants for cutaneous marginal zone lymphoma:
  - Conventional variant (most common)
  - Lymphoplasmacytic variant (previously termed cutaneous immunocytoma)
    * Exclude clinically Waldenstörm macroglobulinemia
  - Plasmacytic variant (also termed cutaneous plasmacytoma)
    * Exclude clinically multiple myeloma
  - Blastoid variant

PCMZL “Conventional Variant”



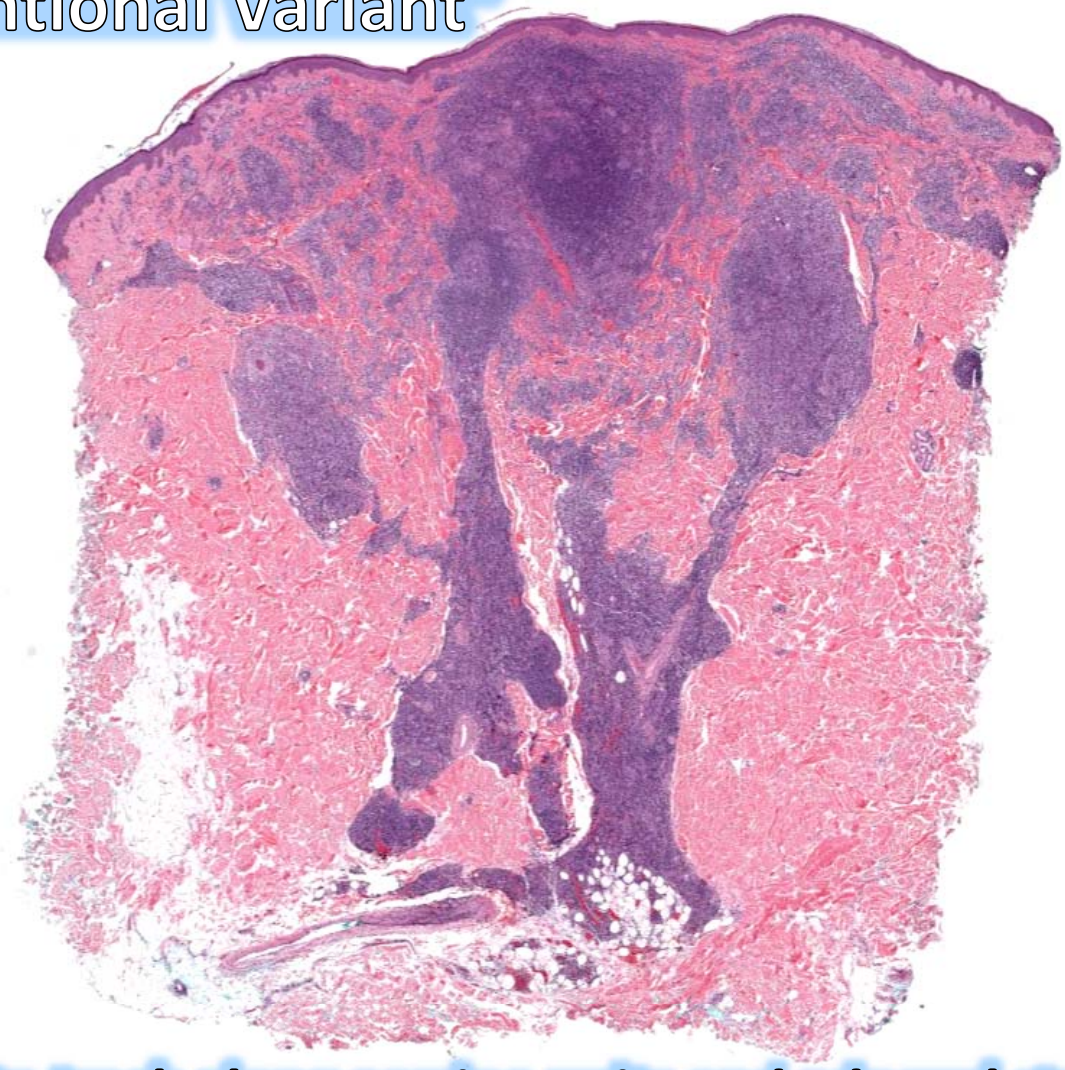
- Can show patchy dermal infiltrate

PCMZL “Conventional Variant”



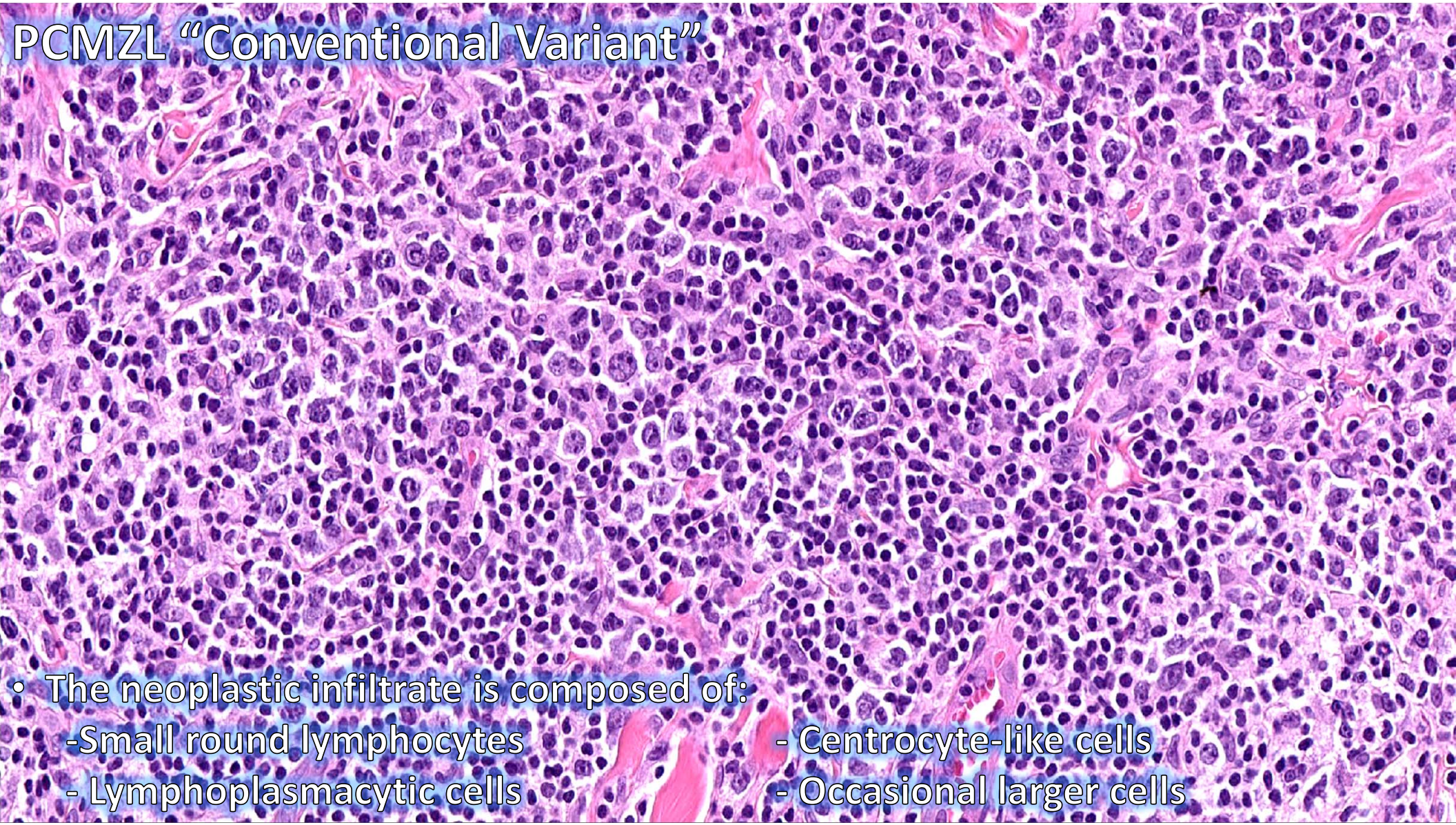
- Can be diffuse/nodular dermal infiltrate and mostly bottom heavy infiltrate
- Dark areas correspond to reactive lymphocytes (can form germinal centers)

PCMZL “Conventional Variant”



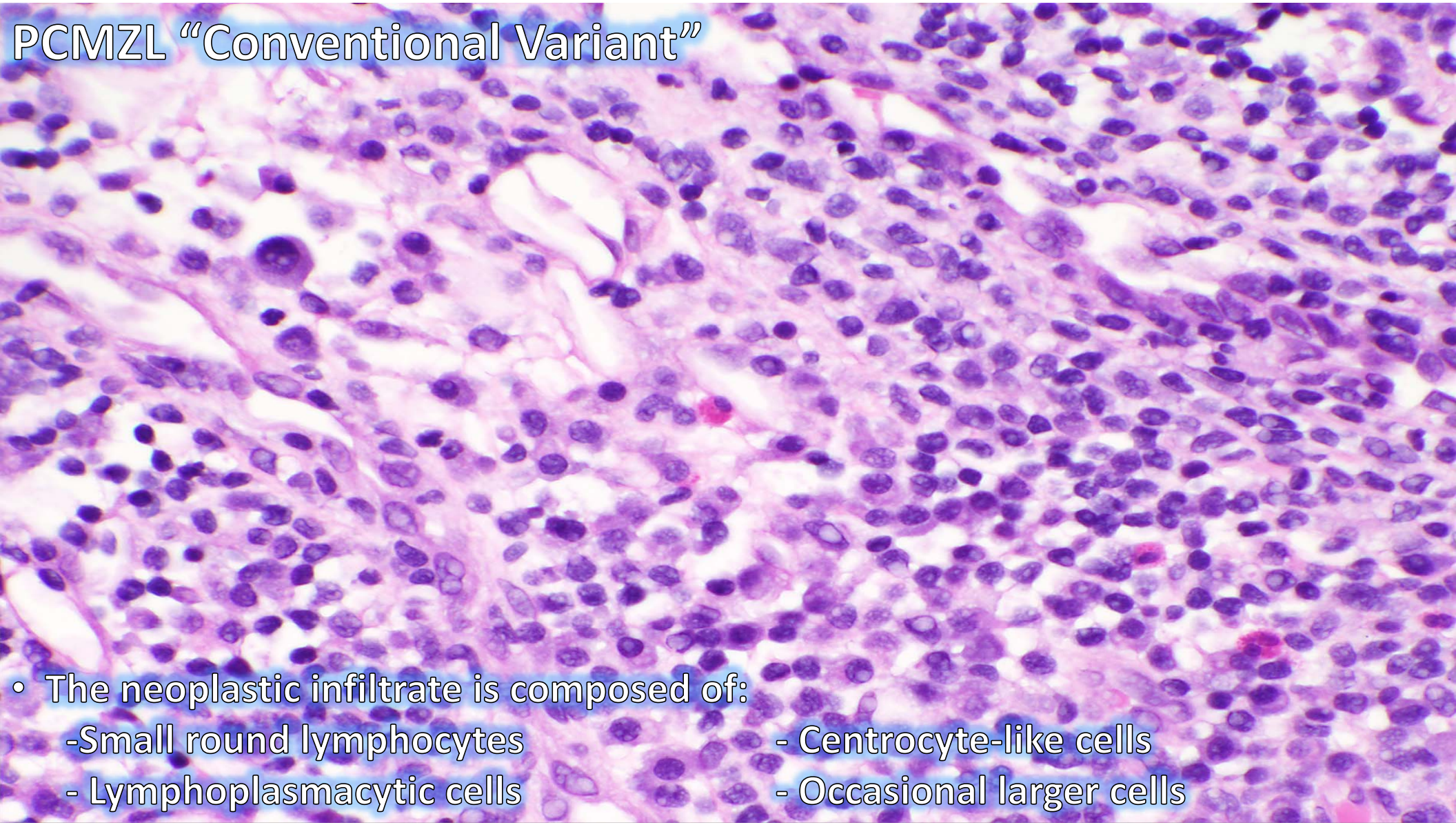
- Have a tendency to track along eccrine units and adnexal structures

PCMZL "Conventional Variant"



- The neoplastic infiltrate is composed of:
  - -Small round lymphocytes
  - - Lymphoplasmacytic cells
  - - Centrocyte-like cells
  - - Occasional larger cells

PCMZL “Conventional Variant”



- The neoplastic infiltrate is composed of:
  - -Small round lymphocytes
  - - Lymphoplasmacytic cells
  - - Centrocyte-like cells
  - - Occasional larger cells

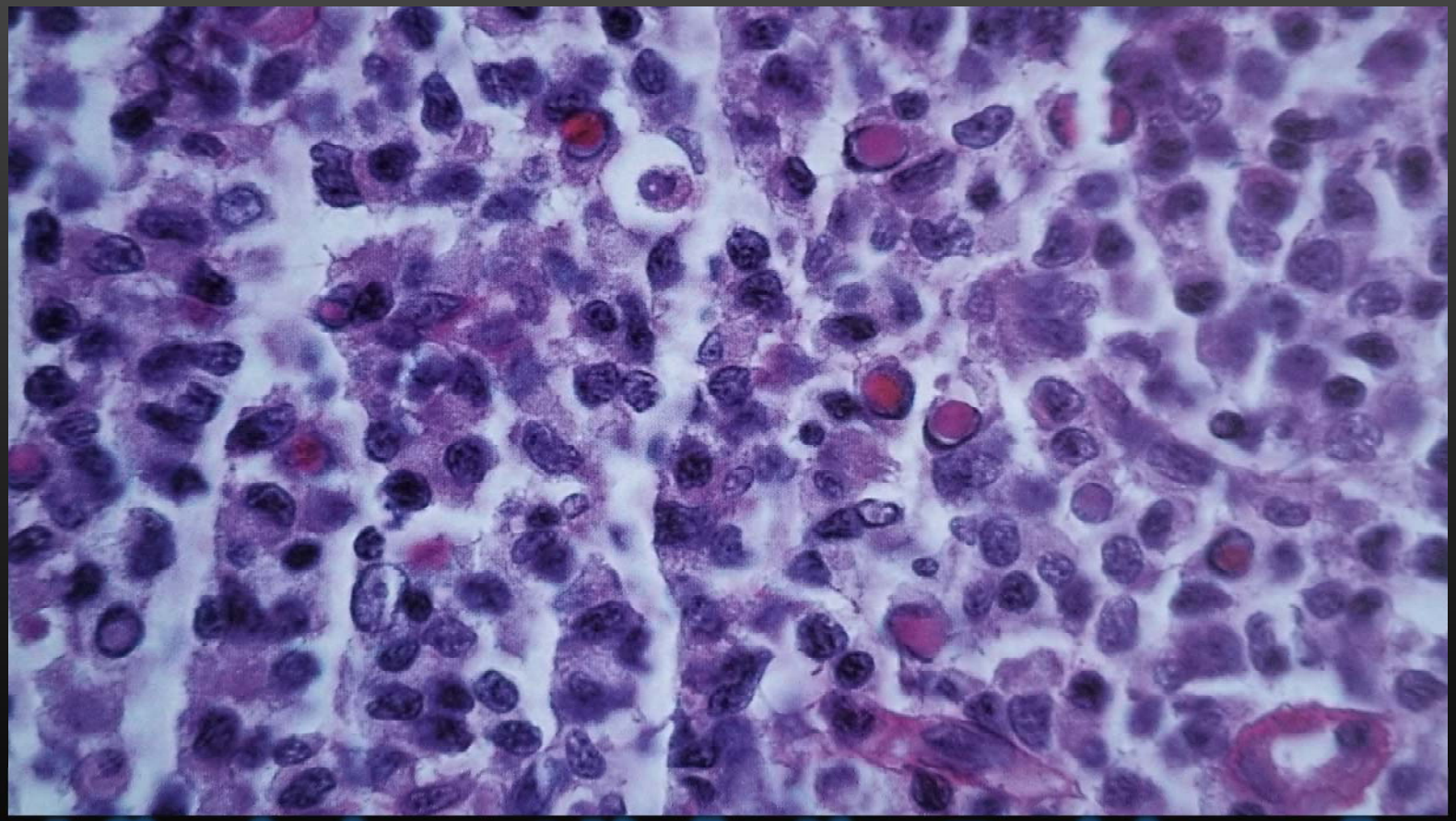
PCMZL “Lymphoplasmacytic Variant”

Skin lymphoma. Figure 12.21

- Dense monomorphic infiltrate
- Does not show mixture with other reactive cells

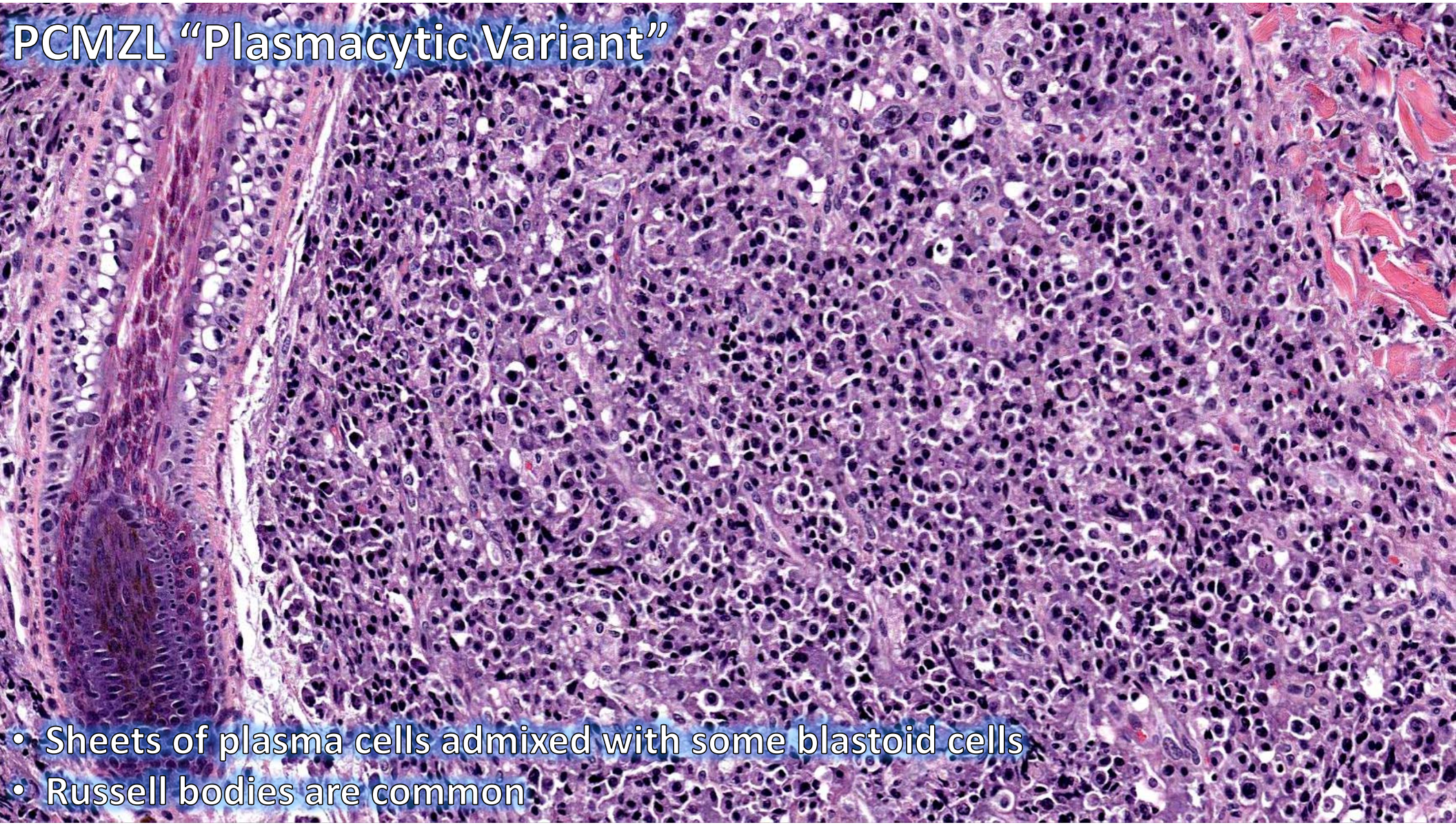
PCMZL “Lymphoplasmacytic Variant”

Skin lymphoma. Figure 12.22



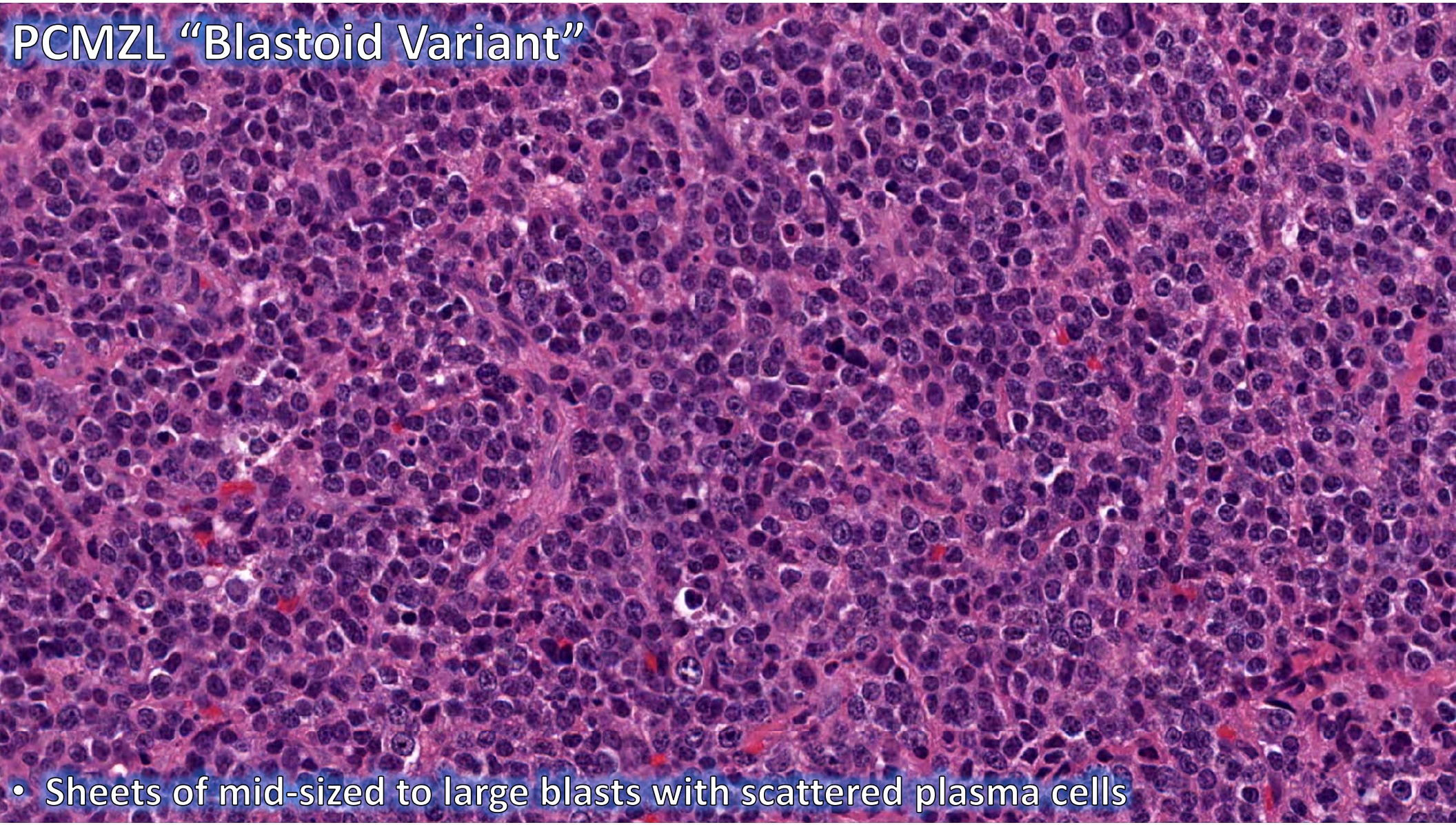
- Composed of lymphoplasmacytoid cells with scattered plasma cells
- The pattern that usually shows “Dutcher bodies”

PCMZL “Plasmacytic Variant”



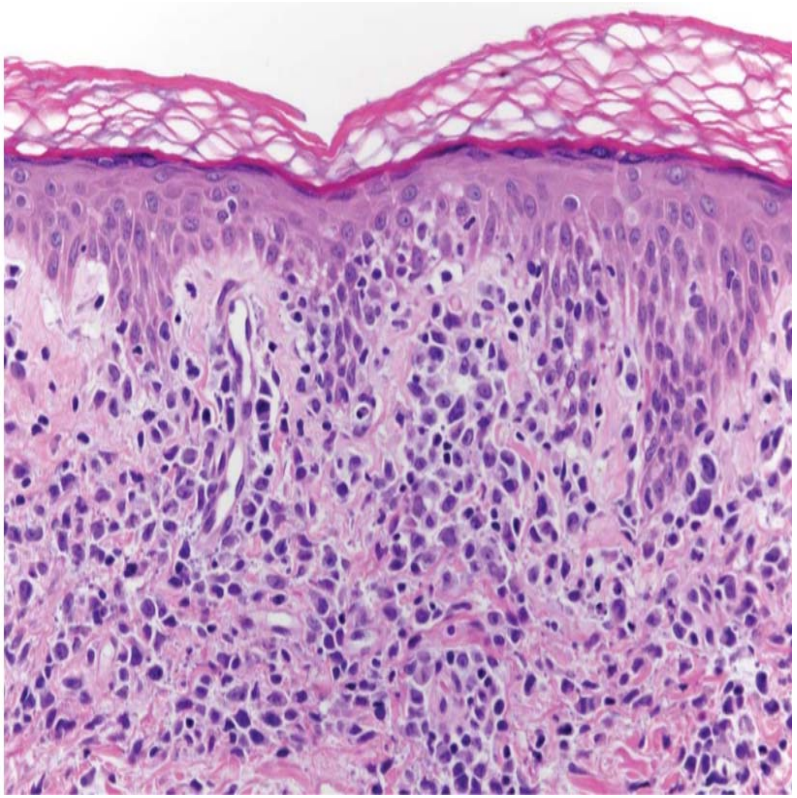
- Sheets of plasma cells admixed with some blastoid cells
- Russell bodies are common

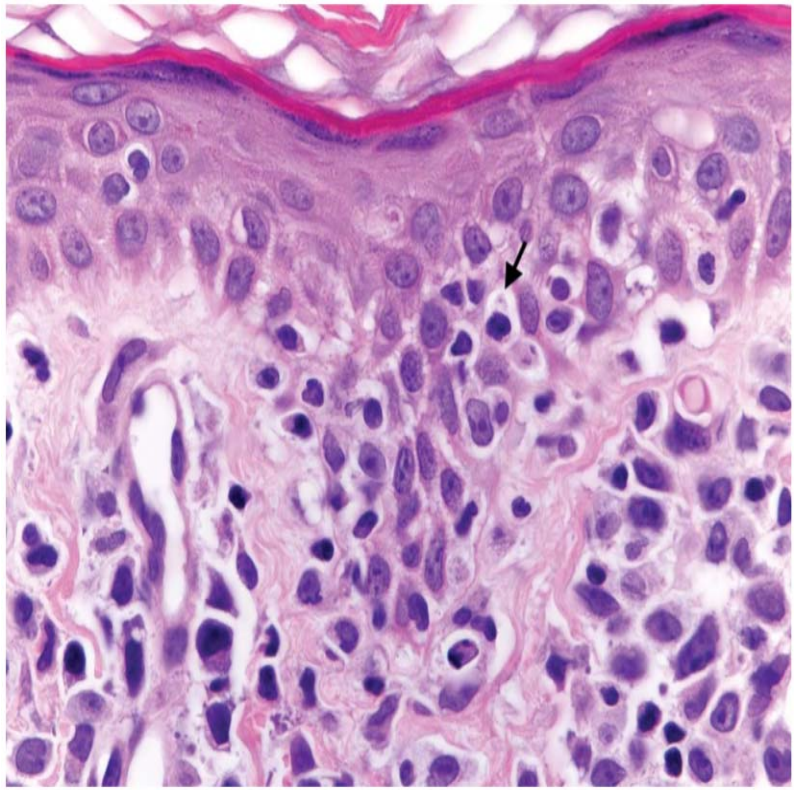
PCMZL “Blastoid Variant”



- Sheets of mid-sized to large blasts with scattered plasma cells

Epidermotropic B-Cell Lymphoma: A Unique Subset of CXCR3-Positive Marginal Zone Lymphoma

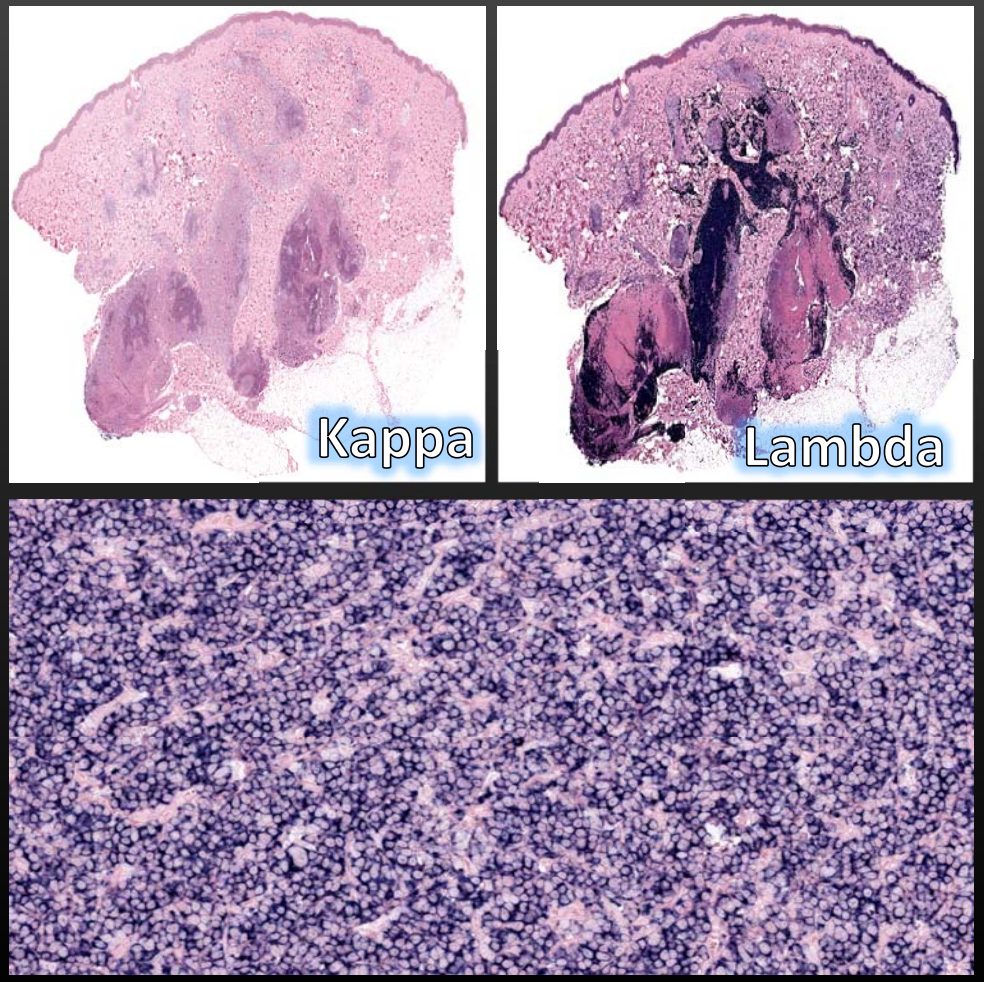




(*Am J Dermatopathol* 2016;38:105–112)

PCMZL Immunohistochemistry

- CD20: Positive in the B cells but negative in the neoplastic plasma cells
- BCL-2: Positive
- CD5, CD10, and BCL-6: Negative
- Monoclonal expression of either kappa or lambda Ig light chain represents the most important feature



PCMZL Molecular

- Monoclonal rearrangement of the immunoglobulin heavy chain genes is present ~50% of cases
- Some studies have shown t(14;18) IGH-MALT-1 and t(3;14) IGH-FOXP1 can be positive in a proportion of PCMZL (less than 20% of cases)
- t(11;18) API-MALT1 and t(1;14) BCL10-IGH are usually negative in cutaneous cases

PCMZL Prognosis

- The prognosis is excellent for most patients without progression for extracutaneous involvement
- Recurrence can be observed in 40 – 50% of patients
- Blastoid variant arising in a patient with a previous history of conventional MZL portends a worse prognosis; however, a de novo presentation of blastoid MZL have an indolent clinical course

  (*Am J Dermatopathol* 2013;35:319–326)

Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type

Diffuse Large B-cell Lymphoma, Leg Type (DLBCL-LT)

- A malignant lymphoma of intermediate behavior
- The nomenclature is mainly for the predilection to affect lower limbs
- They can occur in different sites and carry the same clinical/prognostic profile

Epidemiology of DLBCL-LT

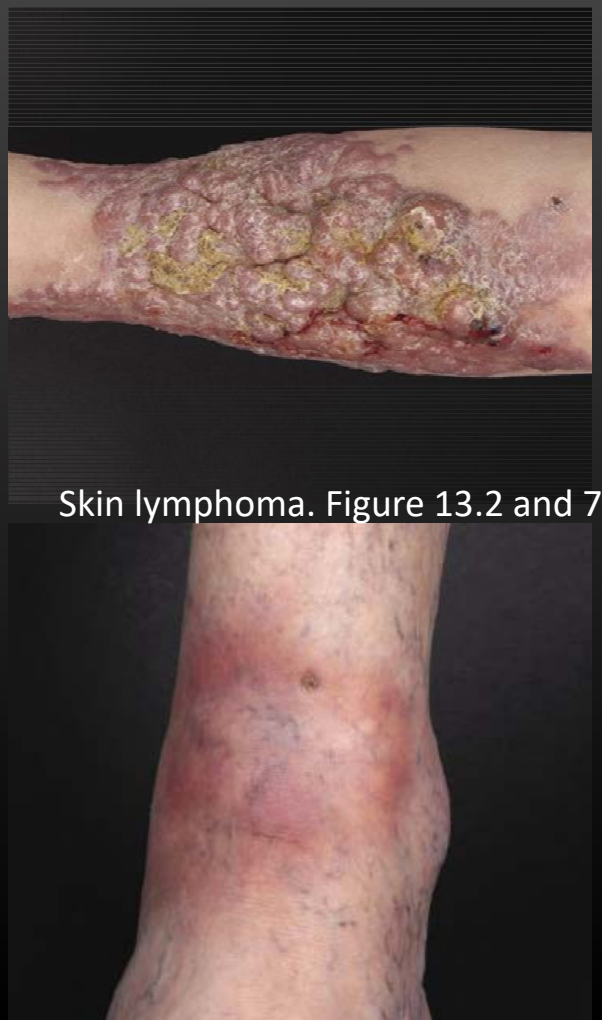
- Accounts for approximately 20% of cutaneous B-cell lymphomas
- Mainly a disease of elderly (>70 years)
- More common in females

Etiology of DLBCL-LT

- Etiology not completely clear
- Can be seen in immunocompromised patients
- *Borrelia burgdorferi* DNA has been demonstrated in rare cases from countries with endemic infection
- Reported cases with positivity for Epstein–Barr virus most likely belong to the category of cutaneous EBV+ diffuse large B-cell lymphoma of the elderly

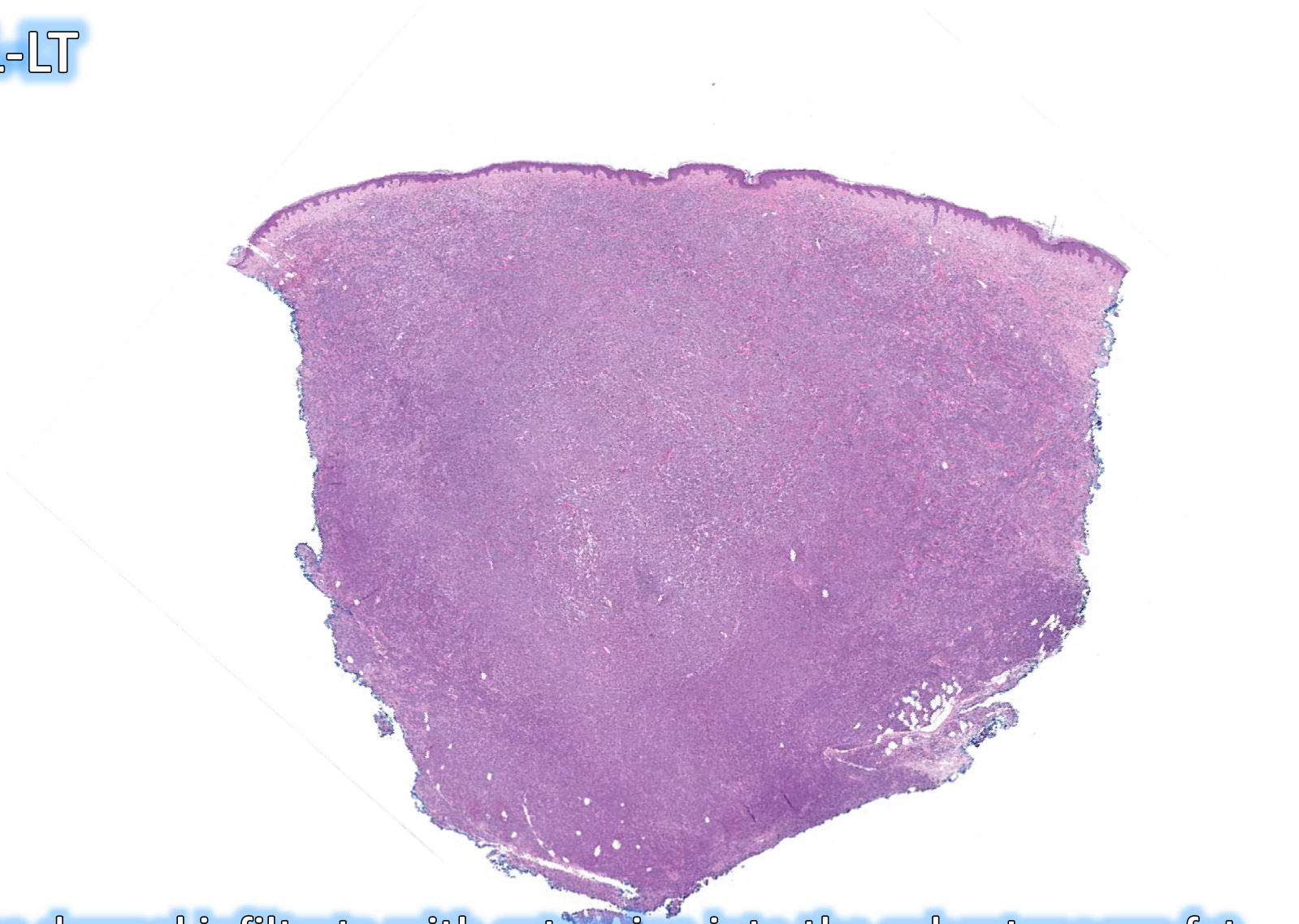
DLBCL-LT Clinical Presentation

- Can sometimes mimic cellulitis/infectious processes clinically delaying diagnosis
- Can present as solitary or localized papules or nodules
- Can arise at cutaneous sites other than the legs in 15-20% of cases

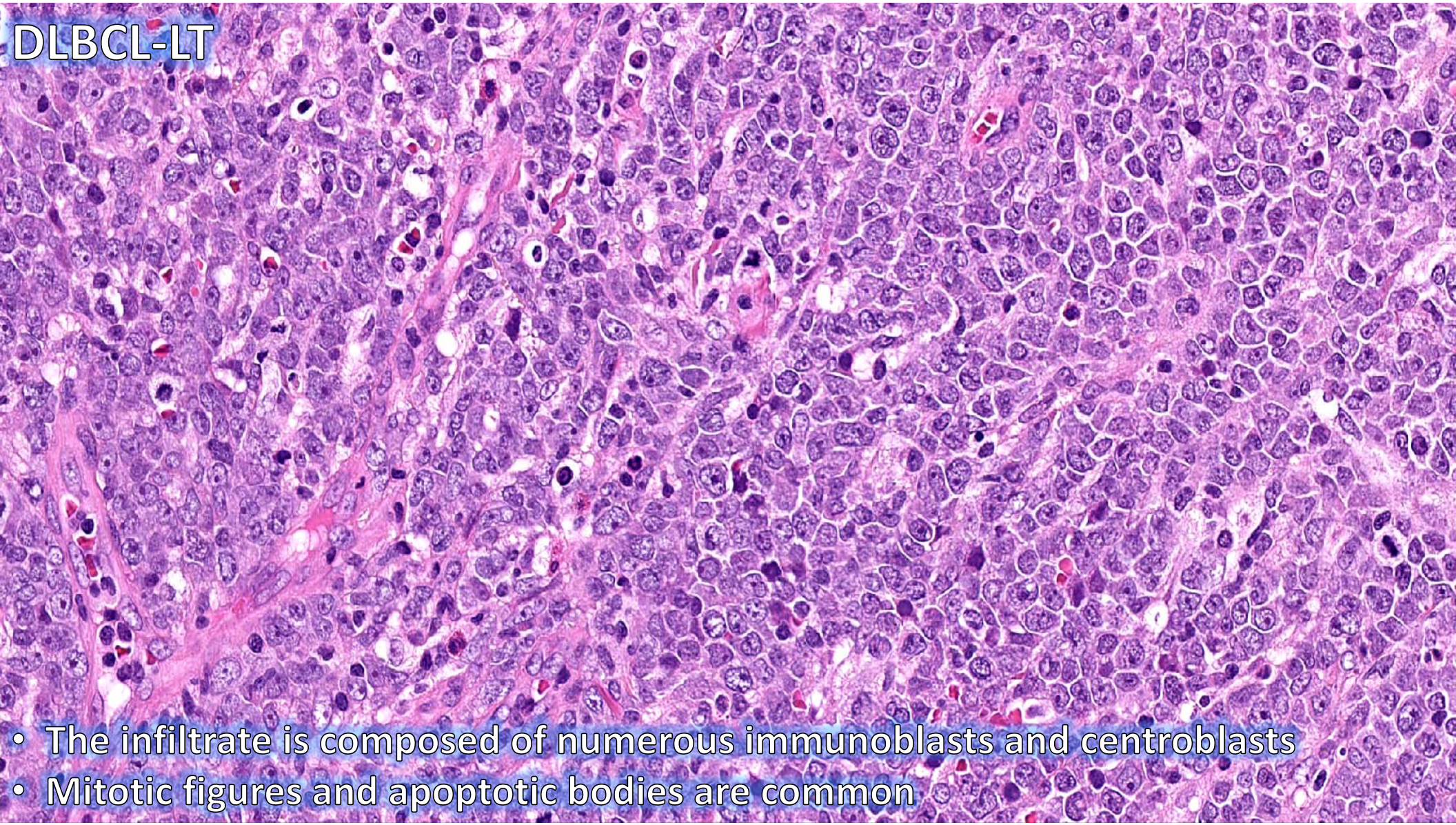


Skin lymphoma. Figure 13.2 and 7

DLBCL-LT

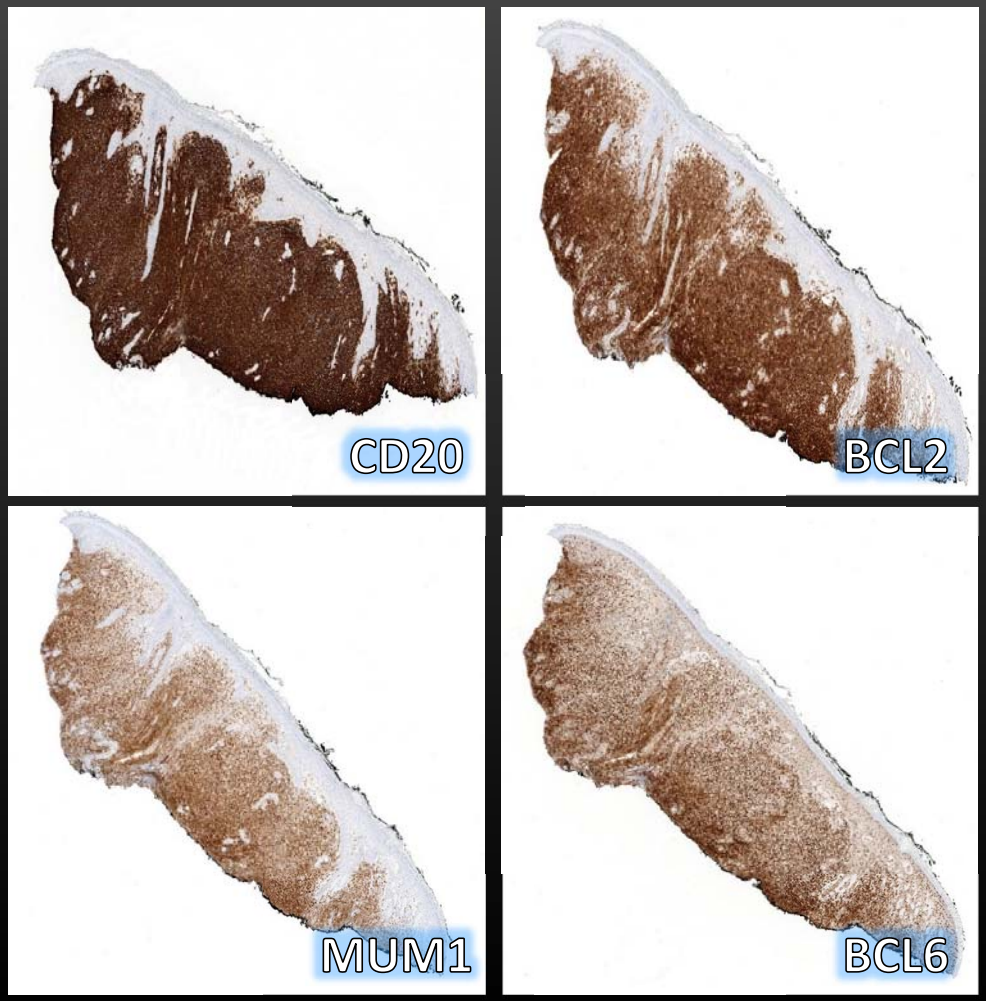


- Diffuse dermal infiltrate with extension into the subcutaneous fat


DLBCL-LT
• The infiltrate is composed of numerous immunoblasts and centroblasts
• Mitotic figures and apoptotic bodies are common

DLBCL-LT Immunohistochemistry

- CD20 and CD79a: Usually diffusely positive but can show partial loss
- BCL-2*, MUM-1, IgM and FOX-P1: Usually diffusely positive (help differentiating from PCFCL)
- Majority of cases express BCL-6 and rarely CD10



DLBCL-LT Molecular

- Monoclonal rearrangement of the immunoglobulin heavy chain genes is found in most cases
- Characterized by a proliferation of post-germinal center cells (activated B lymphocytes)
- No classic translocations

DLBCL-LT Prognosis

- Estimated disease-specific 5-year survival is 40–50%
- Relapse after treatment is common
- Extracutaneous spread often occurs within few years of diagnosis

Other Systemic B-cell Lymphomas with Secondary Cutaneous Involvement

- EBV+ diffuse large B-cell lymphoma of the elderly
- Mantle cell lymphoma
- Burkitt's lymphoma
- Lymphomatoid granulomatosis
- Plasmablastic lymphoma
- Multiple myeloma

Summary

- PCFCL:
  - Diffuse, follicular, and mixed patterns
  - Centrocytes and centroblasts
  - CD20 (+), BCL-6 (+), BCL-2 (+/-), CD10 (+/-), MUM-1 (rare cells)
  - Low-grade except when affecting the legs

- PMZL:
  - Conventional, lymphoplasmacytic, plasmacytic, and blastoid
  - Marginal zone cells, lymphoplasmacytic cells and plasma cells
  - CD20 (+), BCL-2 (+), BCL-6 (-), Monoclonal immunoglobulin
  - Low-grade except when recurrence with blastoid morphology

- DLBCL-LT:
  - Occurs outside the legs in 15-20%
  - Immunoblasts and centroblasts
  - CD20 (+), BCL-2 (+), MUM-1 (+), BCL-6 (+), CD10 (+/-)
  - Intermediate grade lymphoma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