

Atypical Lymphoid Infiltrates



IS IT LYMPHOMA, PSEUDOLYMPHOMA OR SOMETHING ELSE?

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BM, Lymph Nodes, Cutaneous Atypical Lymphoid Infiltrate consultation practice

REFS: Histopathology 2010 Kempf Classification of Cutaneous Lymphomas, an update. Histopathology 2010 Robson Immunohistochemistry and the diagnosis of Cutaneous Lymphomas, 2011 Annals of Oncology Willemze
WHO-EORTC 2005 Classification of Cutaneous Lymphomas
WHO 2008 Classification of HematoLymphoid Neoplasm

Reference Book coming up



- **Non-Neoplastic Hematopathology and Infections**

- [Hernani Cualing](#), [Parul Bhargava](#), [Ramon L. Sandin](#)

- ISBN: 978-0-470-64600-7

- Hardcover

- 600 pages

- February 2012, Wiley-Blackwell

- Many infectious agents disseminate in blood and the lymphatic system, and many of these infections are also tropical diseases that affect a large segment of the world's population, including travelers, immigrants, and refugees. The authors have carefully incorporated in this new book those diseases found in both Western and Eastern hemispheres, in order to assist pathologists and medical laboratory professionals all over the world to better diagnose and treat infections that may be expected, or indeed quite unusual for a given geographic region. The book features a wide range of non-neoplastic hematologic disorders, as well as reactive patterns of non-infectious and infectious agents, all thoroughly illustrated with photographs, tables and text. In addition to the comprehensive and state-of-the-art diagnostic materials, the epidemiology, pathobiology, clinical and pathologic manifestations in blood and lymphatic organs, as well as approaches to treatment, are also described.

Objectives

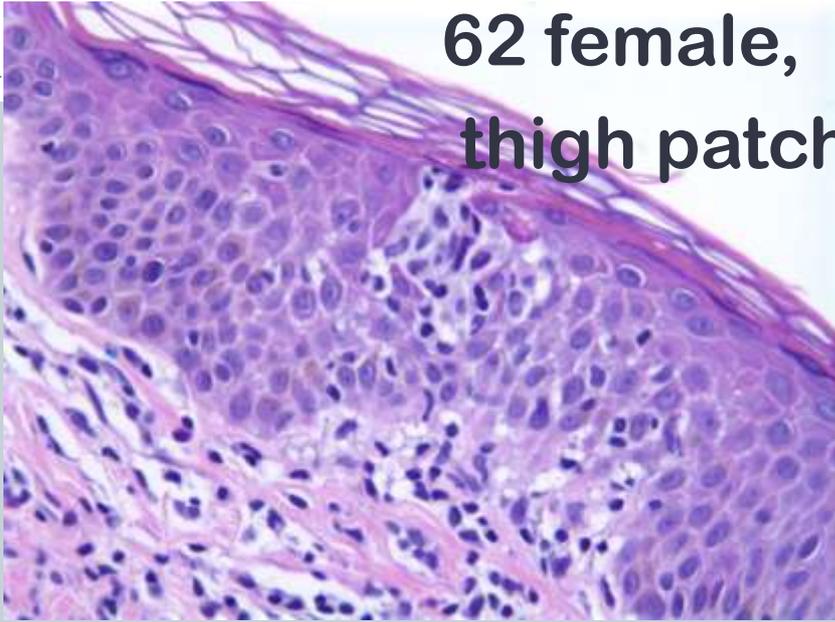


- To go over cutaneous atypical infiltrates work up in order to facilitate diagnosis by showing:
 - Exemplary cases seen in cutaneous hematopathology subspecialty practice
 - Using an approach to diagnosis based on appearance and cell markers

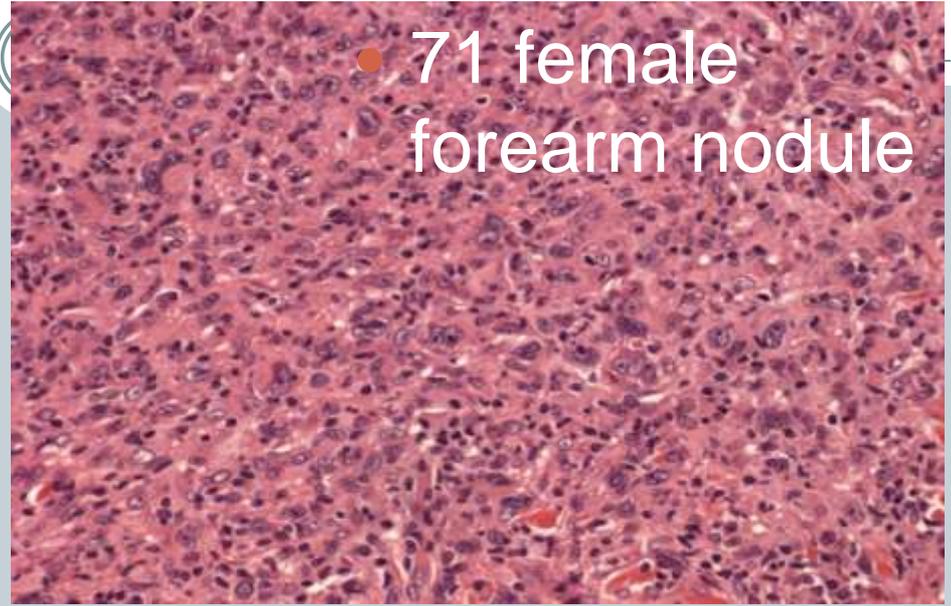
atypical cutaneous lymphoid infiltrate?

The CD3 CD20 negative phenotype

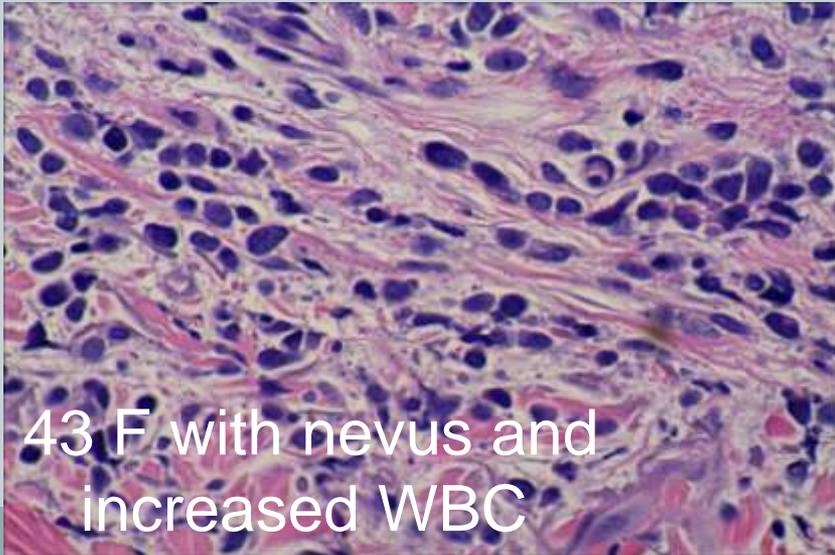
62 female,
thigh patch



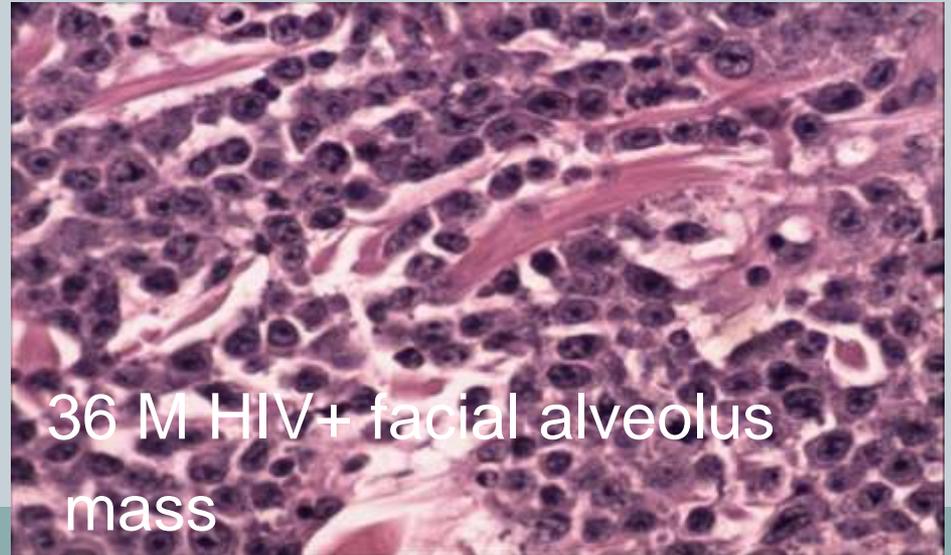
71 female
forearm nodule



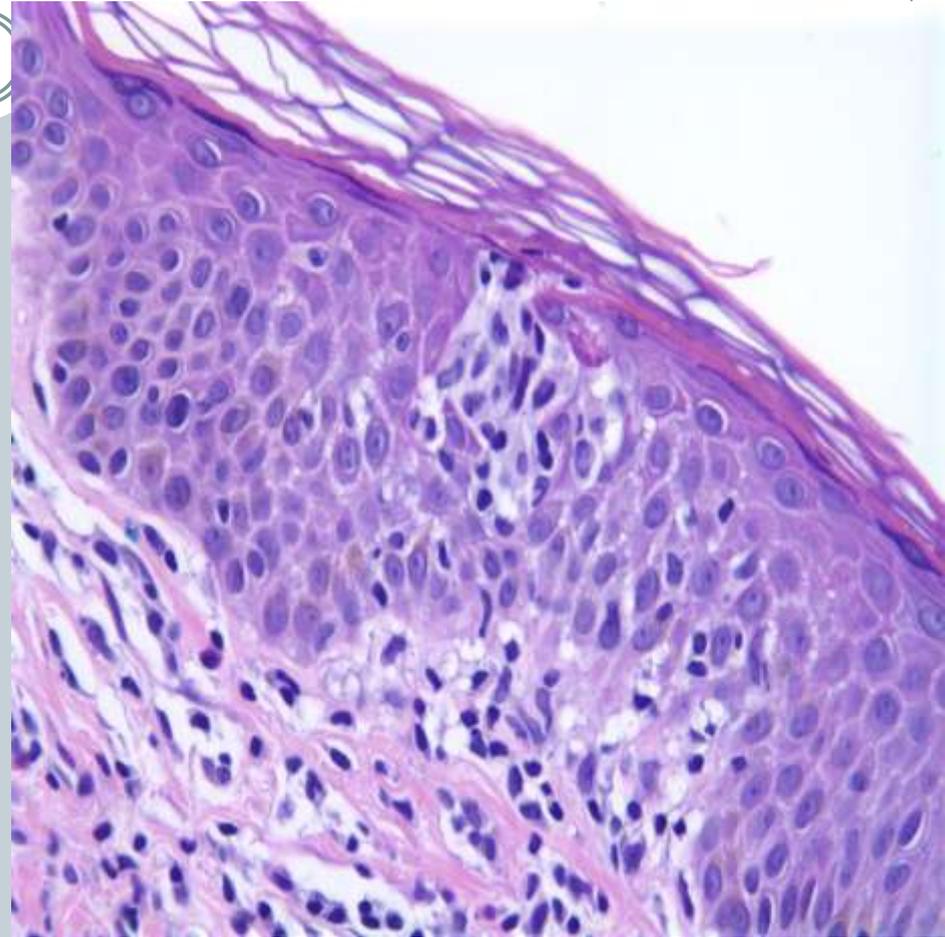
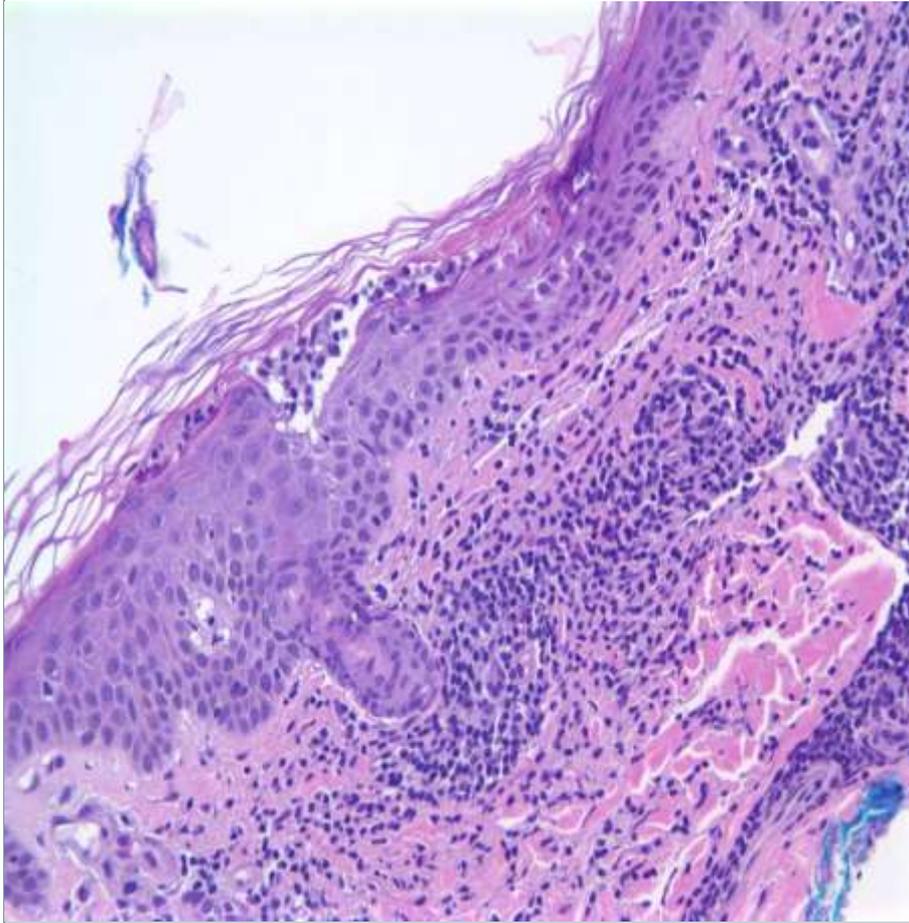
43 F with nevus and
increased WBC



36 M HIV+ facial alveolus
mass

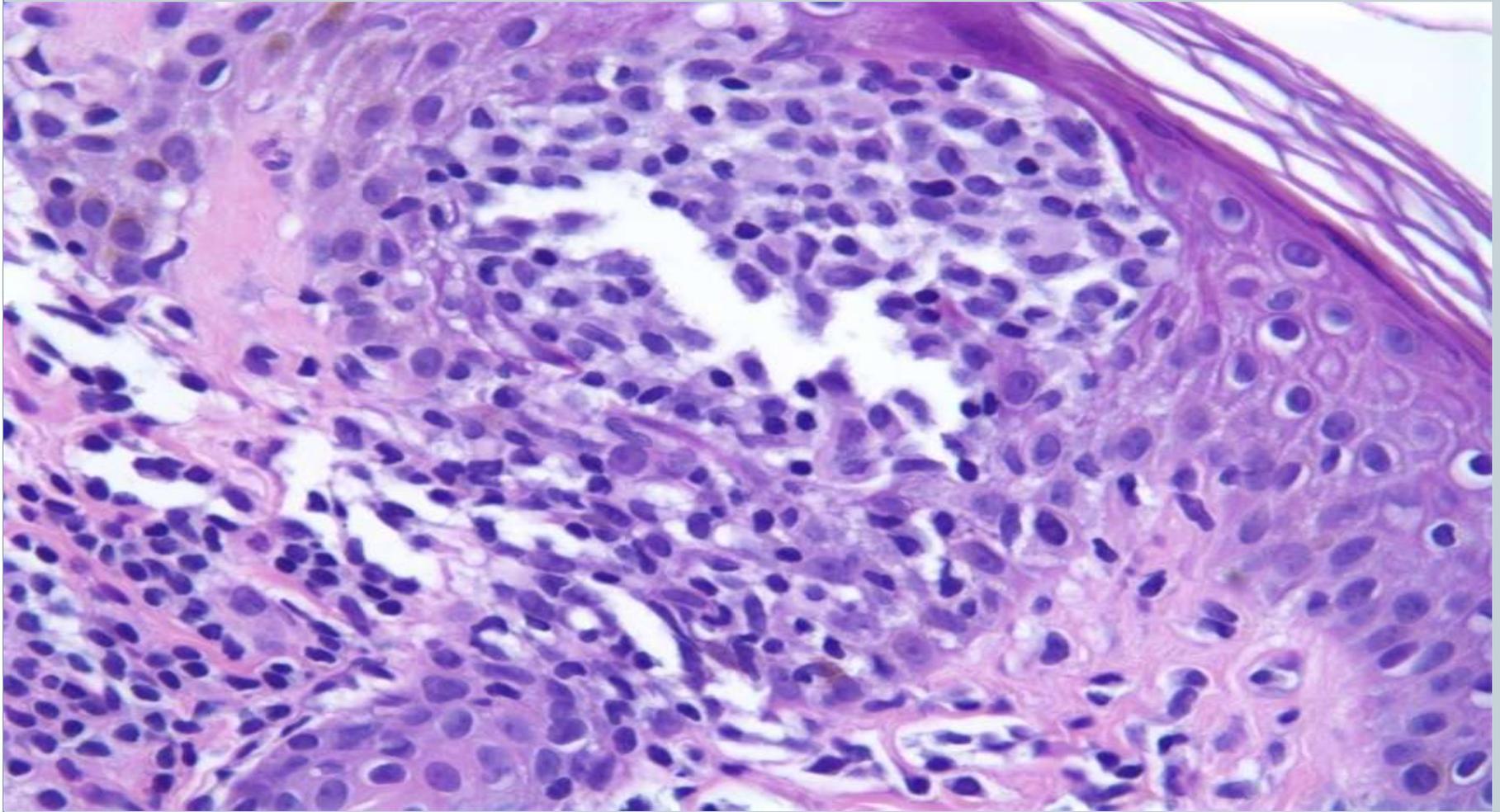


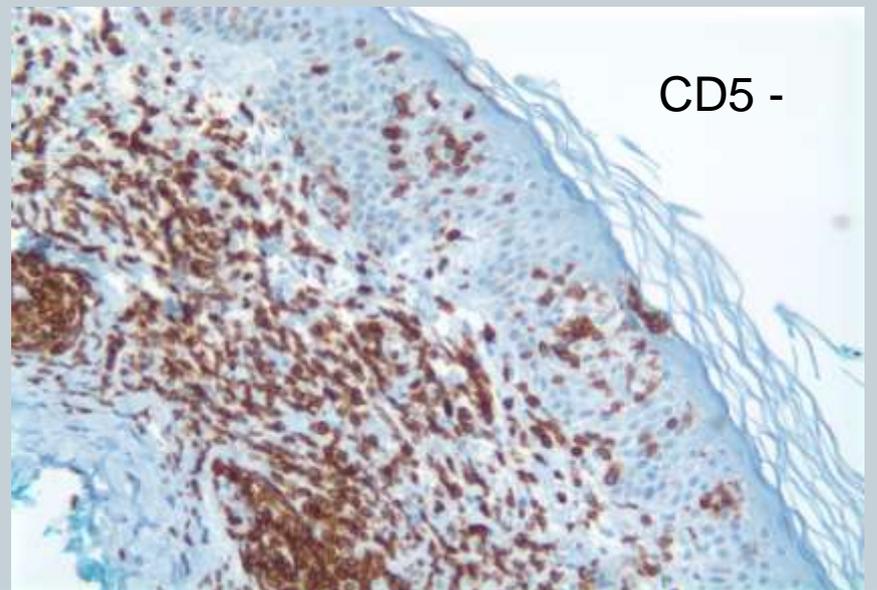
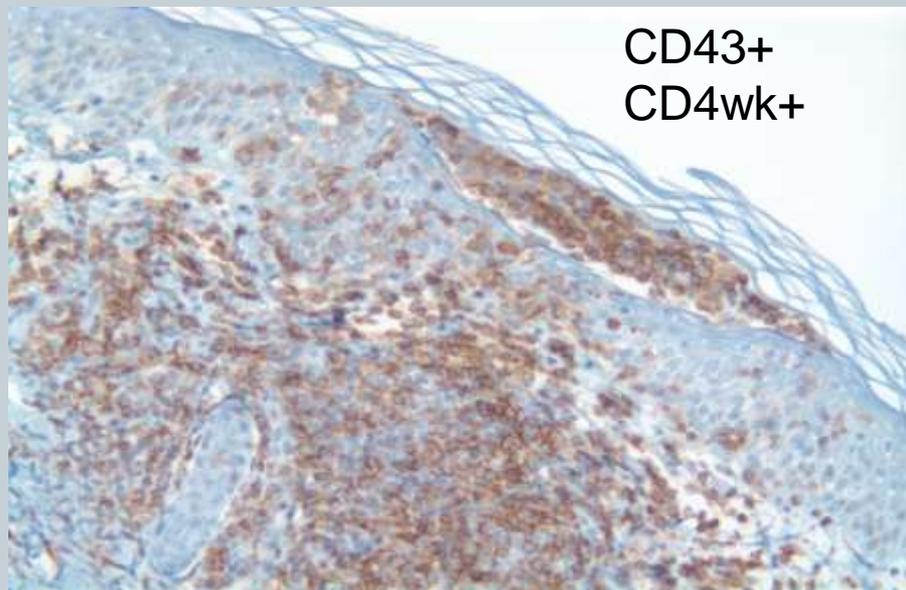
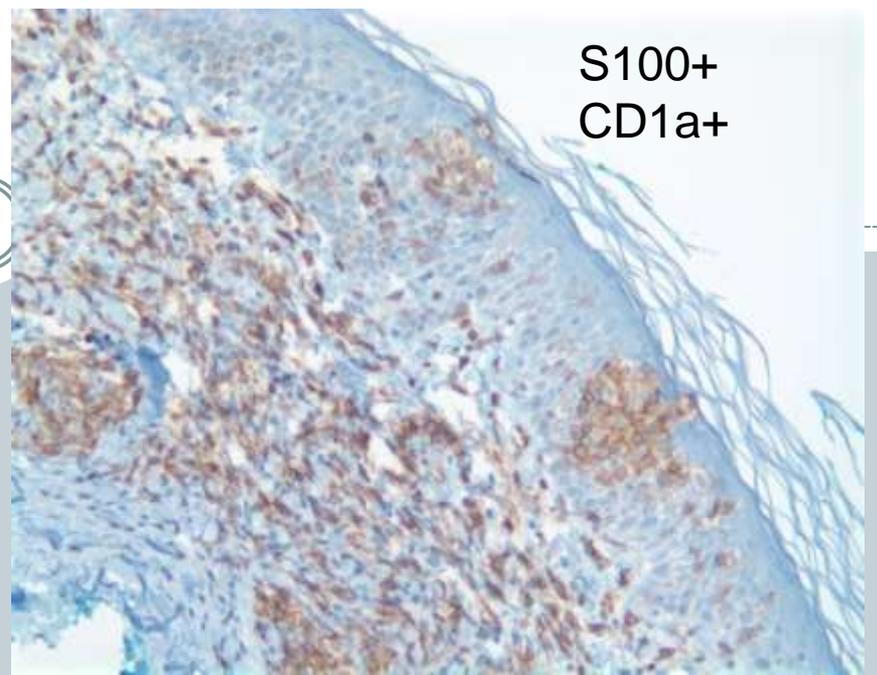
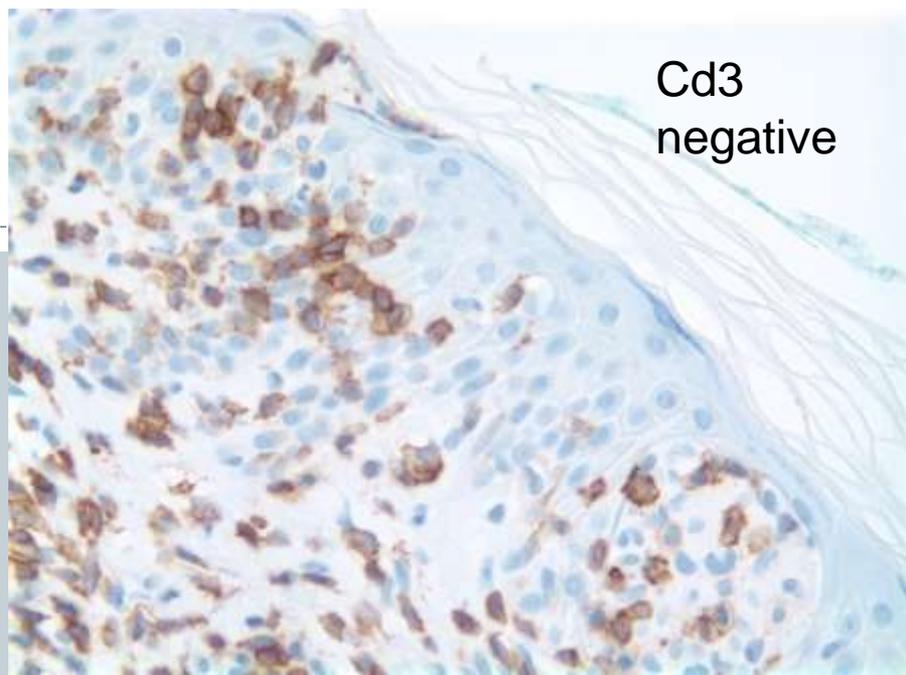
histopathology



- Perivascular lichenoid pattern with epidermotropic collections

High power view of nests





Histiocytic Disorders Immunophenotype by Cell Type



- **Antigen presenting histiocytic cells**

	CD45	CD1a	S100	CD21	CD35	FactorXIII
• <i>Langerhans cell</i>	+	+	+	-	-	-
• Follicular dendritic	-	-	±	+	+	-
• <i>Interdigitating</i>	+	-	+	-	-	-
• Dendrocyte (dermal)	+	-	-	-	-	+
• Indeterminate	+	±	+	-	-	-

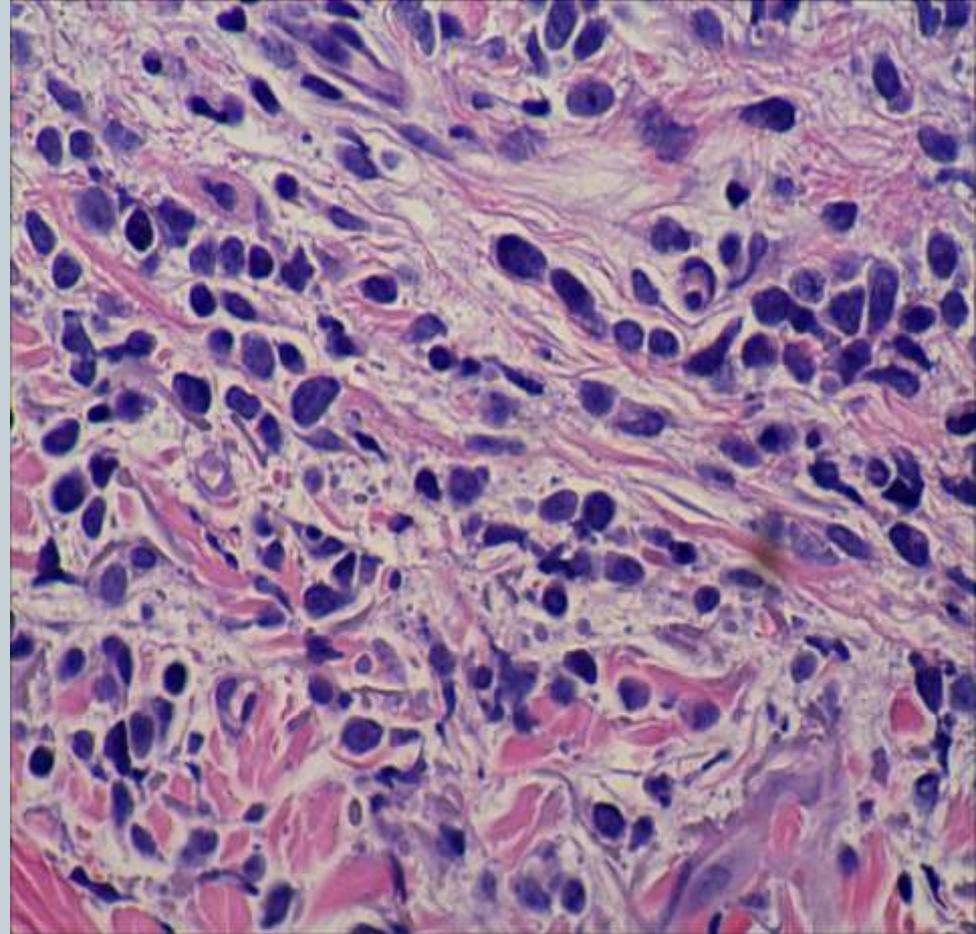
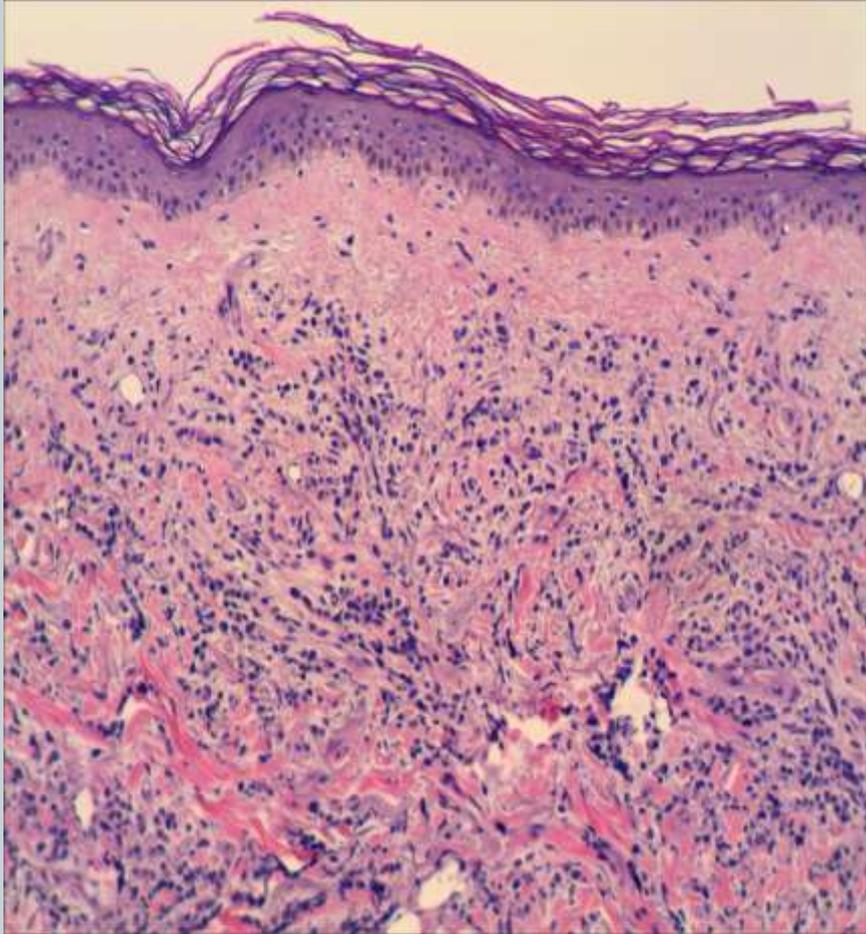
- *Source: Adapted from Onciu (2004).*

Langerhans cell hyperplasia

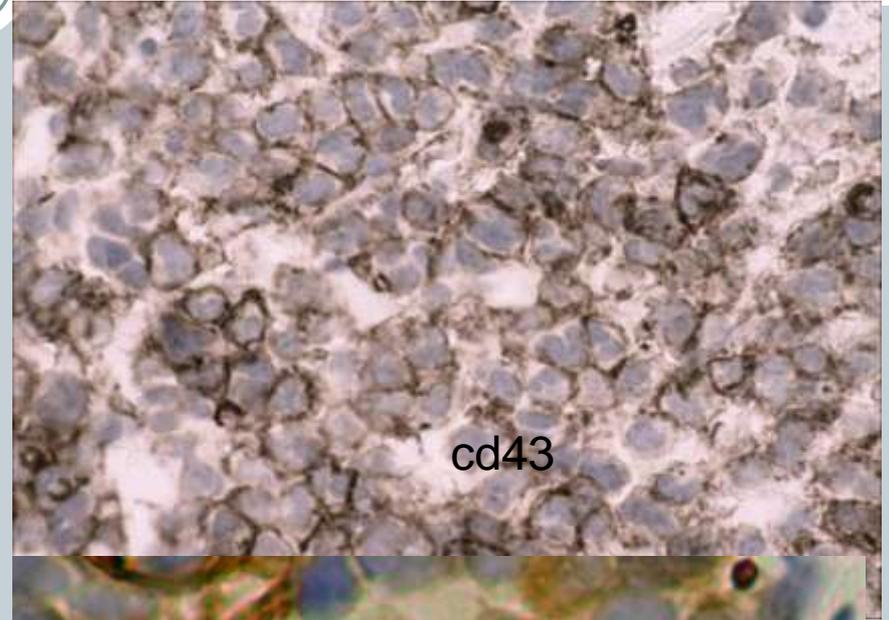
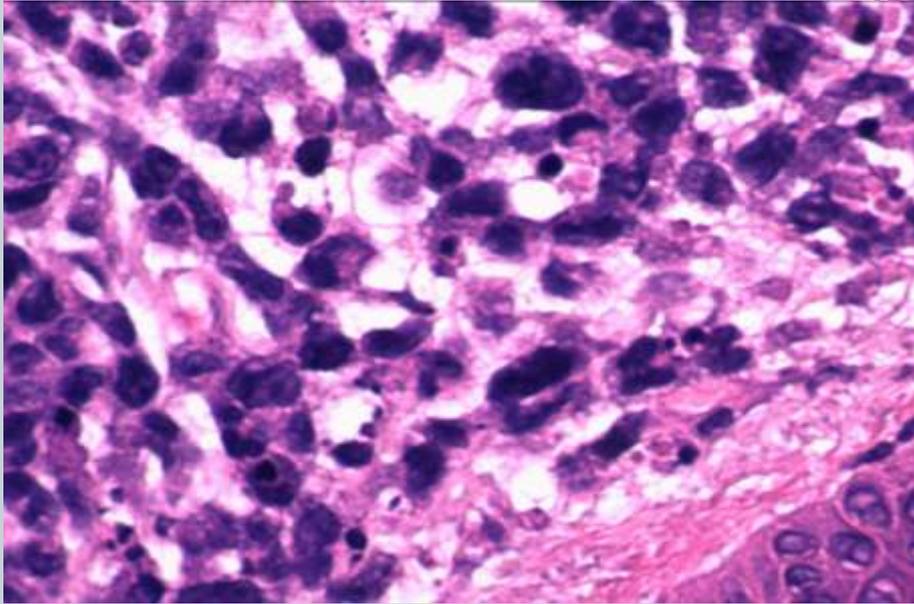


- The Langerhans cell is named after Paul Langerhans, Because of their dendritic appearance, he thought these cells part of the nervous system- close Skin sentinel cells –stratum spinosum = 2 to 4% scattered, seen as collections in:
 - Scabies, atopic dermatitis, leprosy, tuberculosis.
 - Neoplasms- MF
- LNs and extra nodal tissue
- Benign, may be mistaken for Pautrier's abscess, may be associated with certain infections and tumors

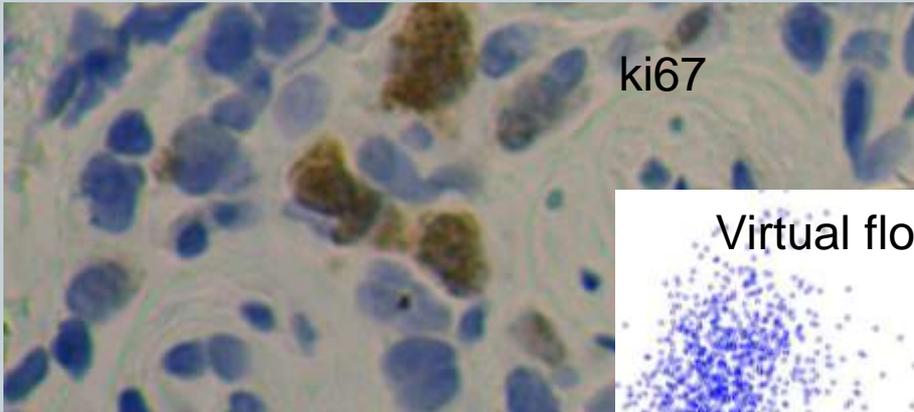
43 female



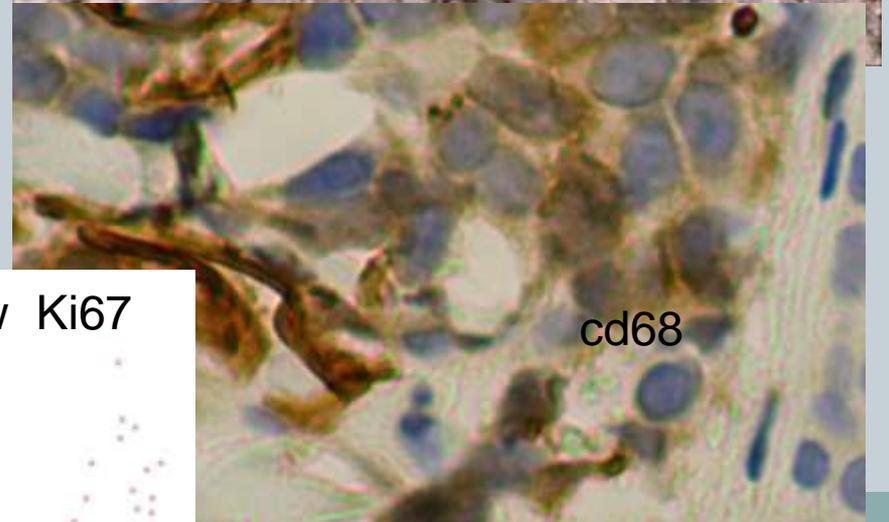
Myeloid sarcoma (chloroma)



cd43

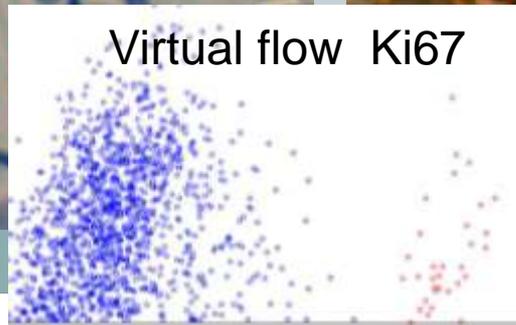


ki67



cd68

Virtual flow Ki67

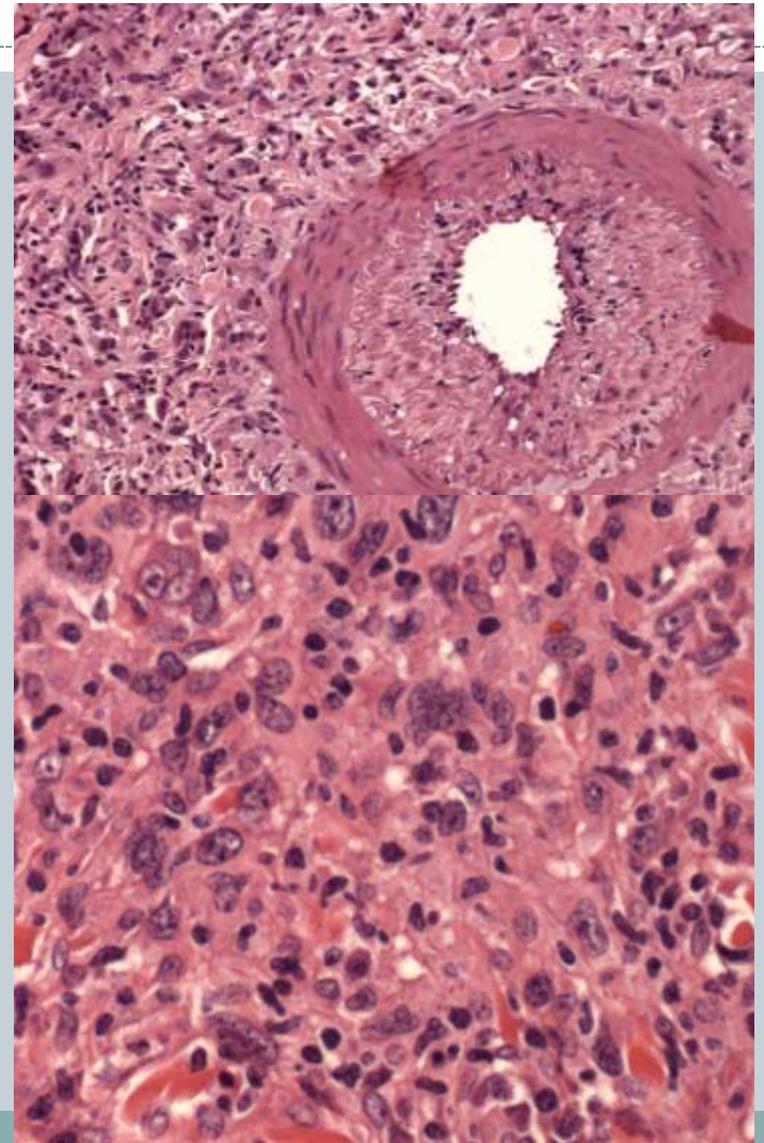


MS or Extramedullary myeloid tumor

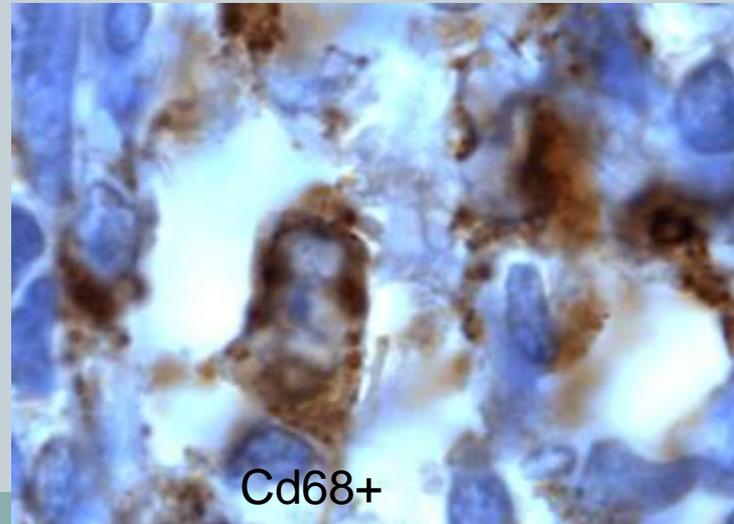
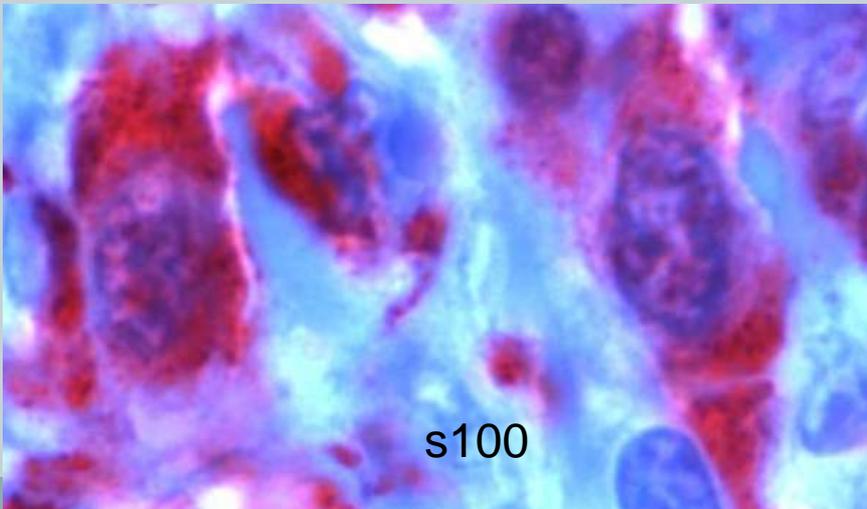
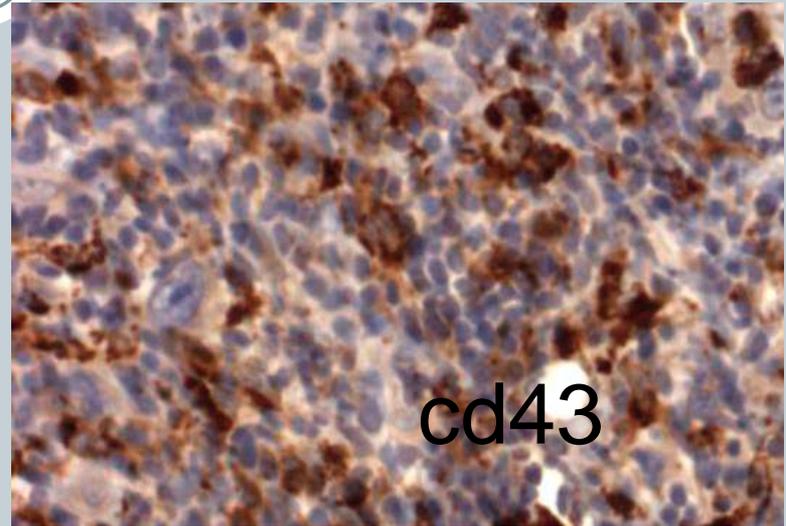
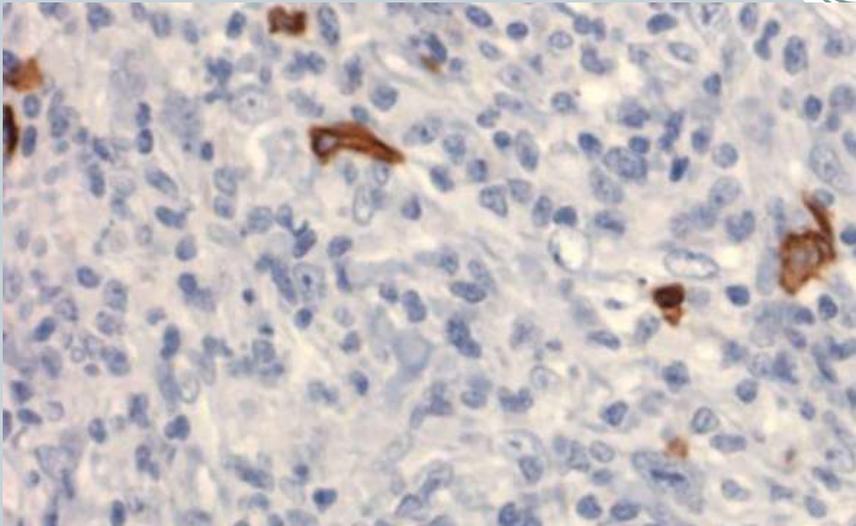


- Common in skin
- Can happen before, during and after AML, CML or MDS
- Can be differentiated or Blastic
- May rarely show blasts cell markers CD34 or Tdt
- Clues: nests of single file, figurate tumor cells
- Subclassification is best done by work up of blood or bone marrow, NPM1 mutation in 1 of 6
- CD3 negative, CD43 positive phenotype
- Comprise about 13 % of cases I see in referral

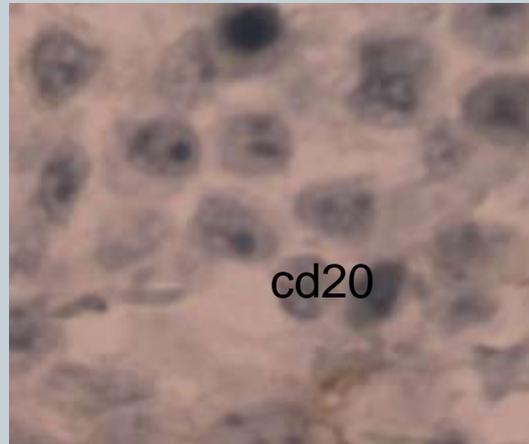
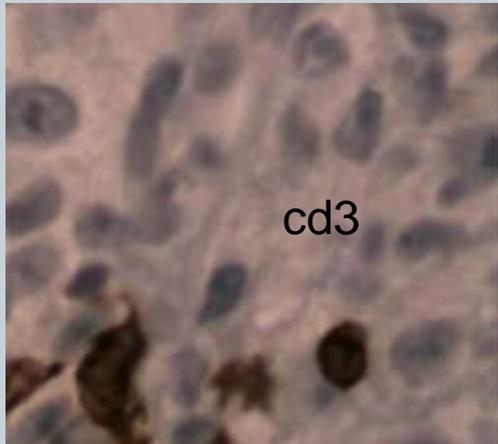
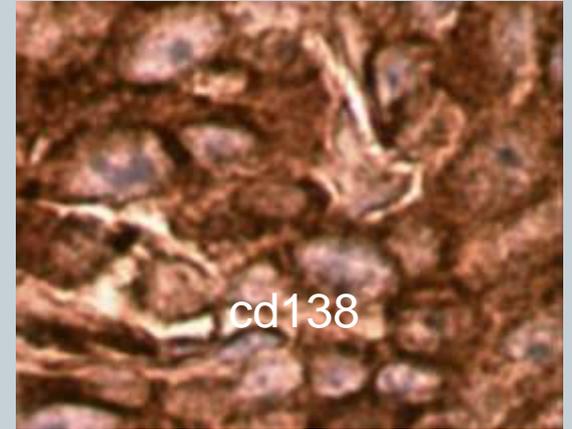
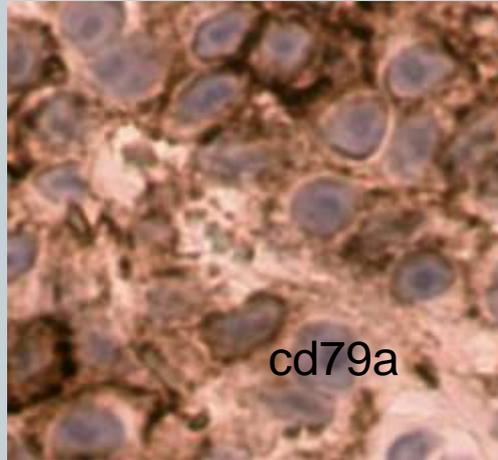
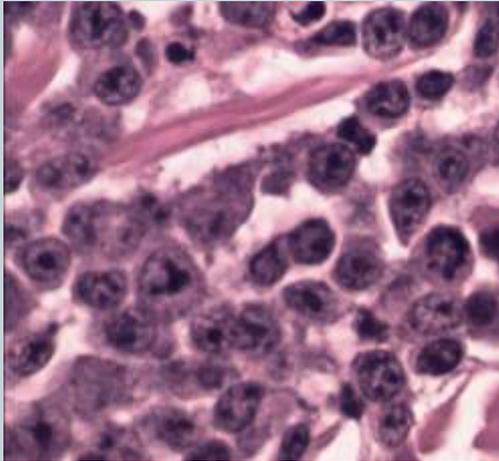
71 female scalp mass



Dendritic cell vs melanocytic neoplasm

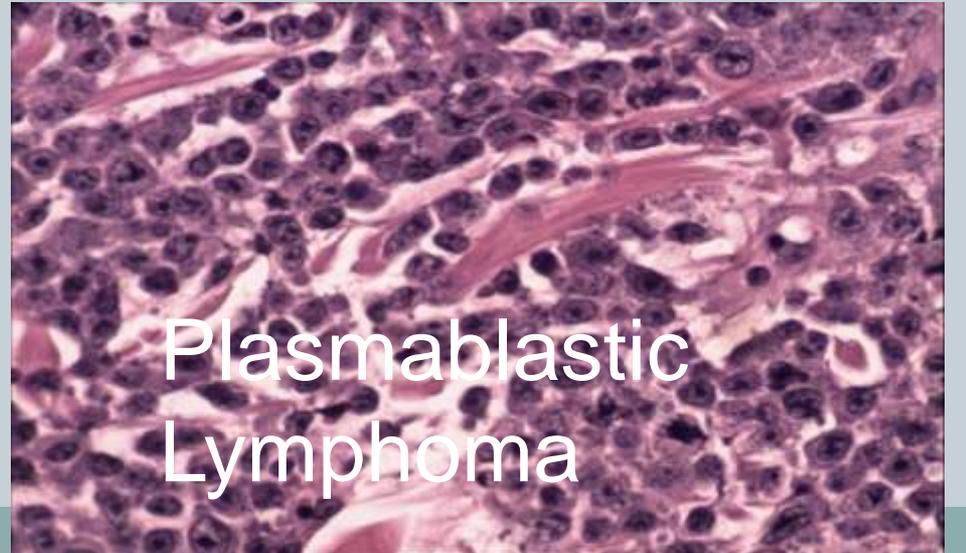
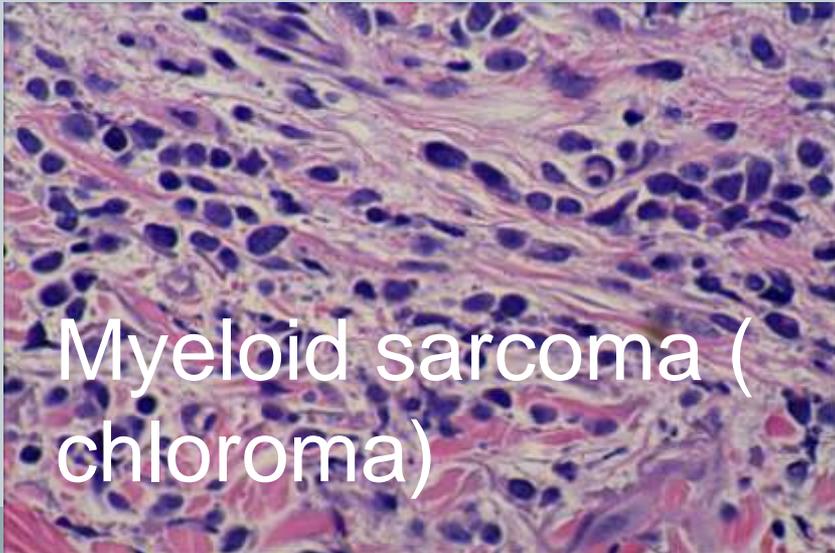
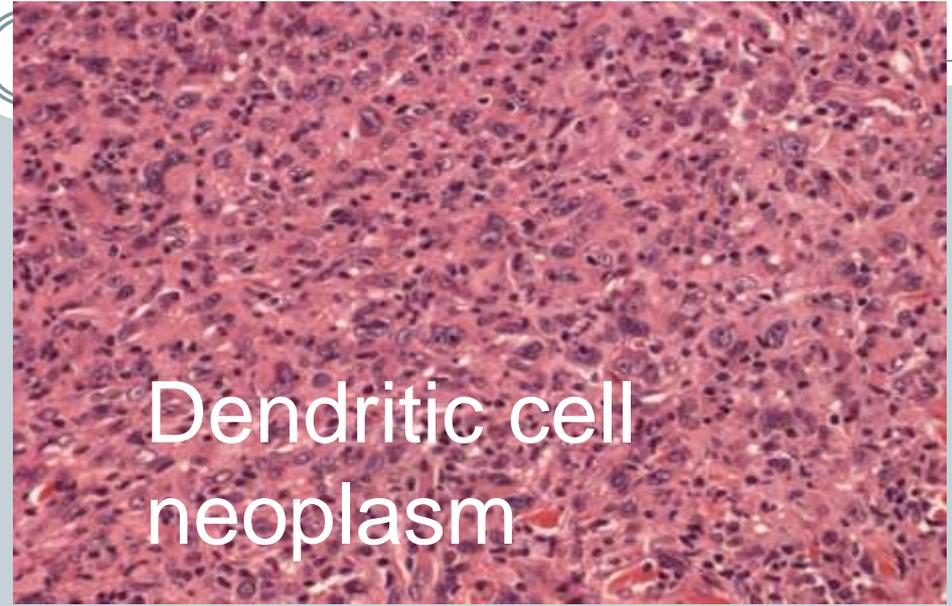
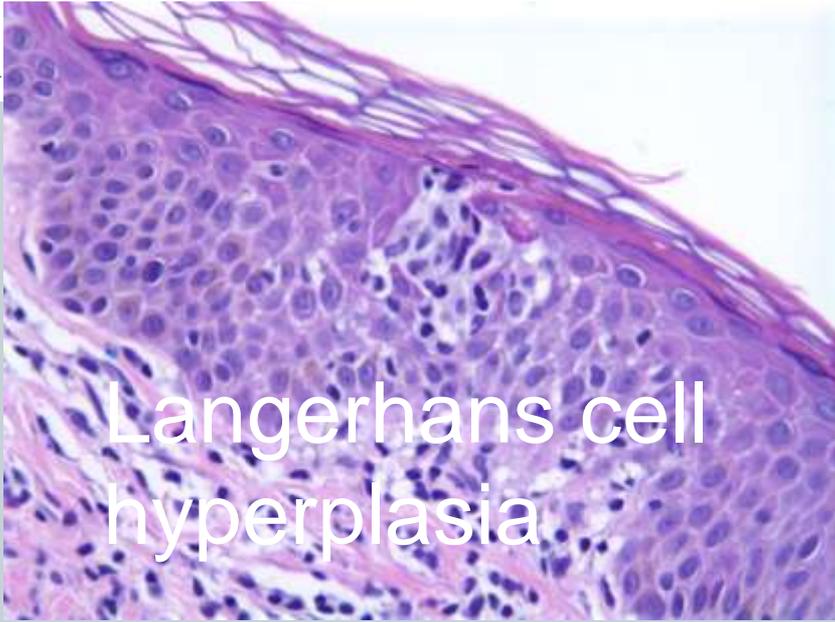


Plasmablastic Lymphoma



Epstein Barr
virus in situ
hybridization +

The CD3 CD20 negative phenotype



The CD3 (20)negative CD43 positive phenotype



- Langerhans cell hyperplasia
- Dendritic cell neoplasm
- Myeloid sarcoma (chloroma)
- Plasmablastic Lymphoma

Case distribution



● Cutaneous B cell lymphoma	24.6%
● Cutaneous T cell lymphomas	18.2%
● CD30 Lymphomas	5.1%
● Myeloid sarcoma etc	12.7%
● Cutaneous Pseudolymphoma	25%
● Real atypical Clonal CLH	5.0%
● Secondary lymphoma	1.2%
● Others miscellaneous	7.0%

Primary Cutaneous B-cell lymphomas*28.5

Follicle center cell lymphoma	8.5 %
Marginal zone B-cell lymphoma	7.1
Diffuse large B-cell lymphomas,leg-type	2.6
Diffuse large B-cell lymphomas,other	8.8
Intravascular large B-cell lymphoma	
Plasmablastic lymphoma	
T cell rich B cell lymphomas	
other rare types	

*SEER USA data 2009, Blood 113:5064, 3884 cases (100%)

CUTANEOUS B CELL LYMPHOMA



	5 yr survival
a. Prim Cut Follicle center cell lymphoma	95%
b. Prim Cut Marginal Zone lymphoma*	77%
c. Diffuse large B-cell lymphoma, leg type**	41%
d. Diffuse large B-cell lymphoma, other	50%
e. PC Intravascular large B-cell lymphoma	56%

*ArchDerm 2005; 141, 1139 Clin Therapy Features of 50 cases, Relapse free SR after complete remission Solitary 77%, Multifocal 39% ; ** Arch Derm 2007, 143:1144

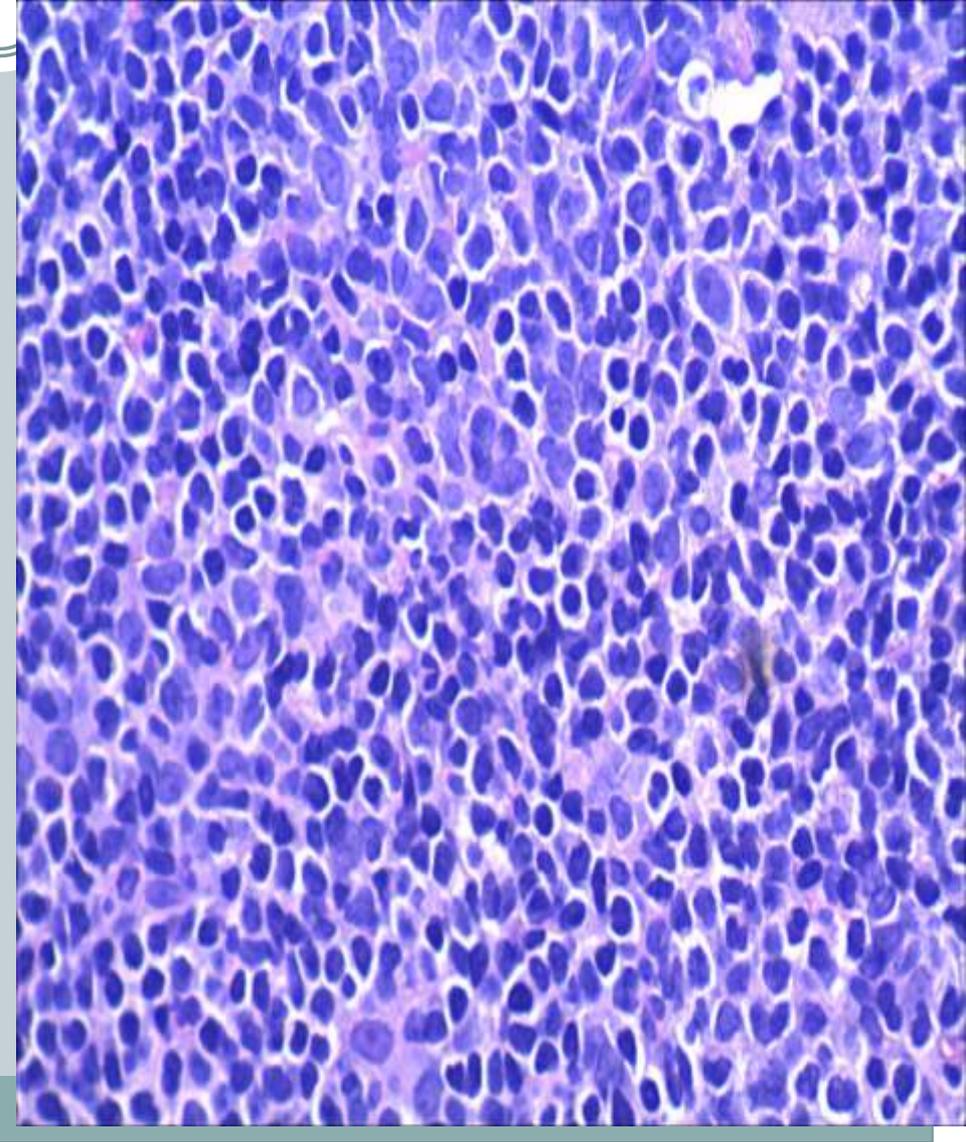
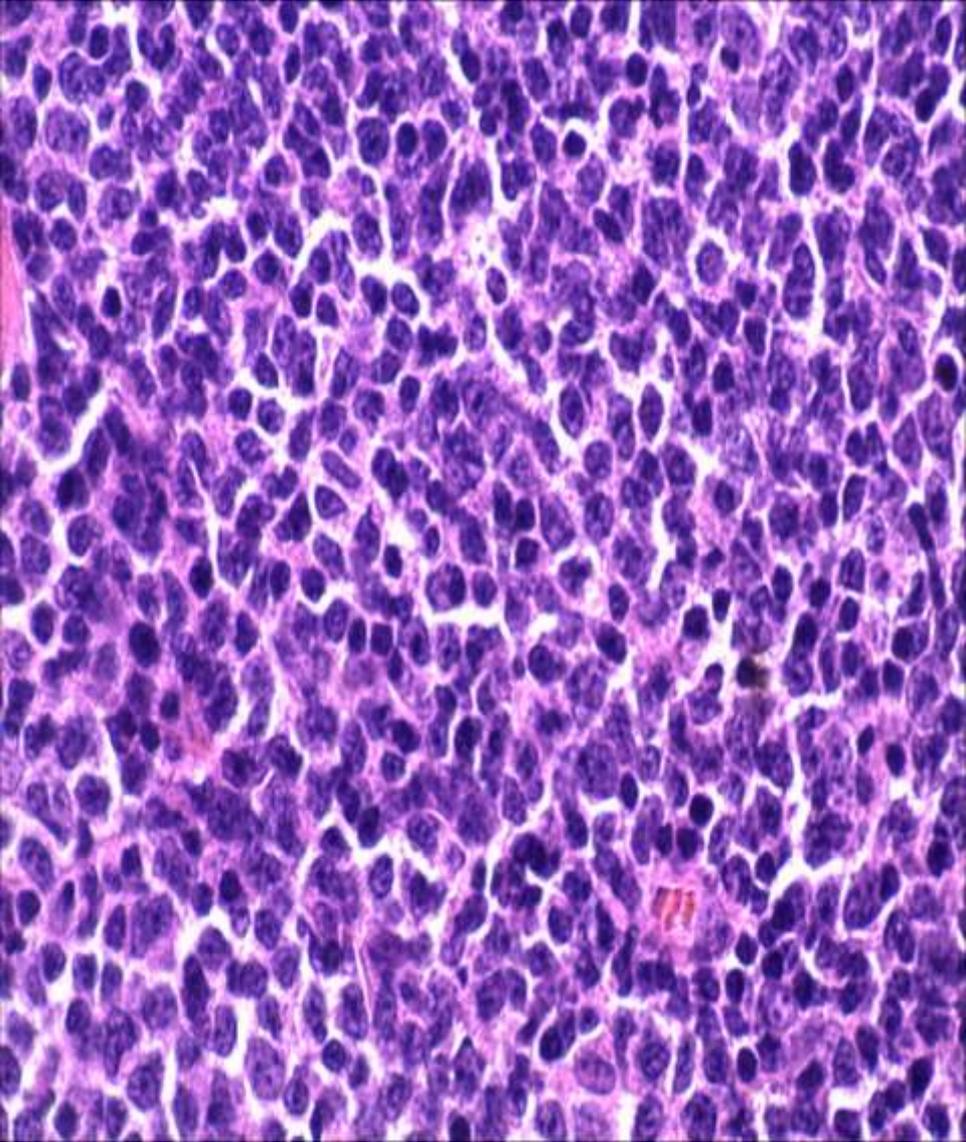
ALL other data: WHO-EORTC 2005

CD20 predominant phenotype

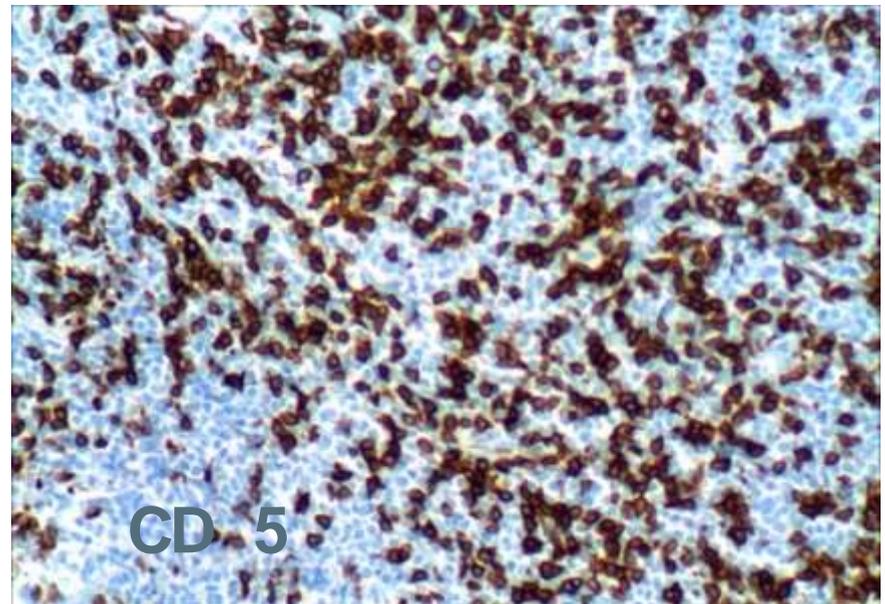
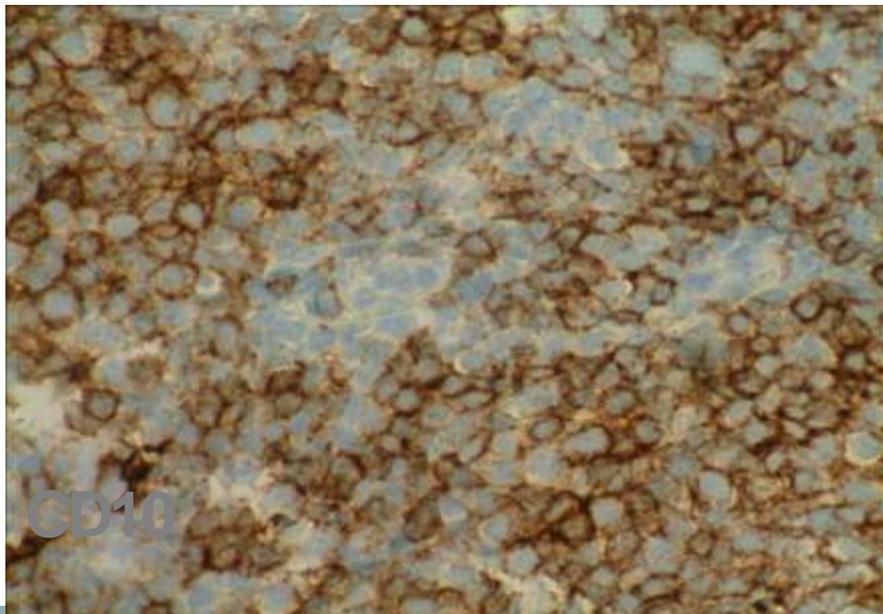
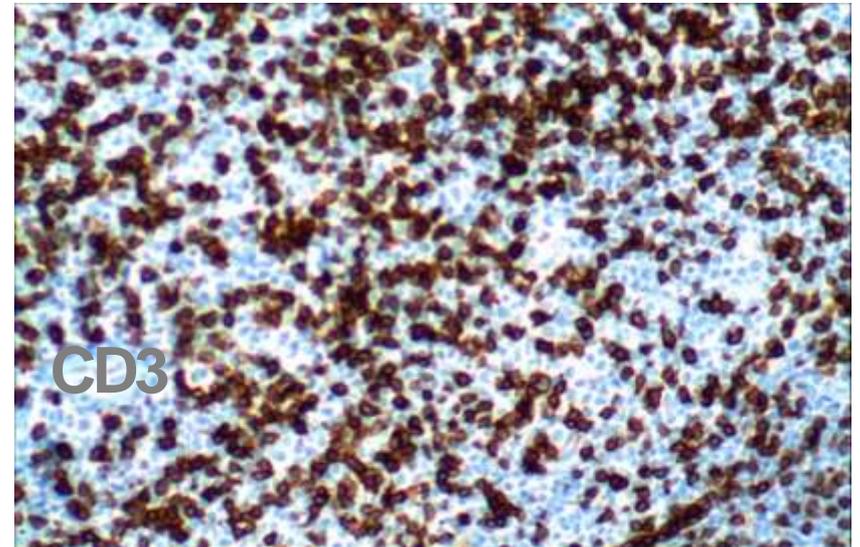
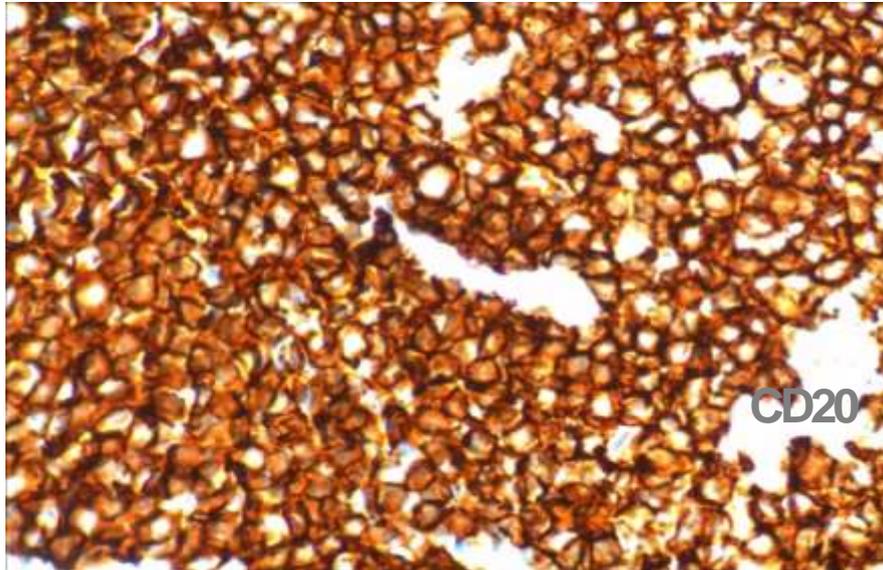


- **Cutaneous B cell lymphoma 24.6%**
 - Marginal zone lymphoma 5.0%
 - Follicle center cell, F/D 5.0%
 - DLBCL Leg type 1.2%
 - DLBCL, Other 5.0%
 - Immunocytoma 2.5%
 - SECONDARY , ie, CLL 2.5%
- **Cutaneous B cell Pseudolymphoma 3.8%**

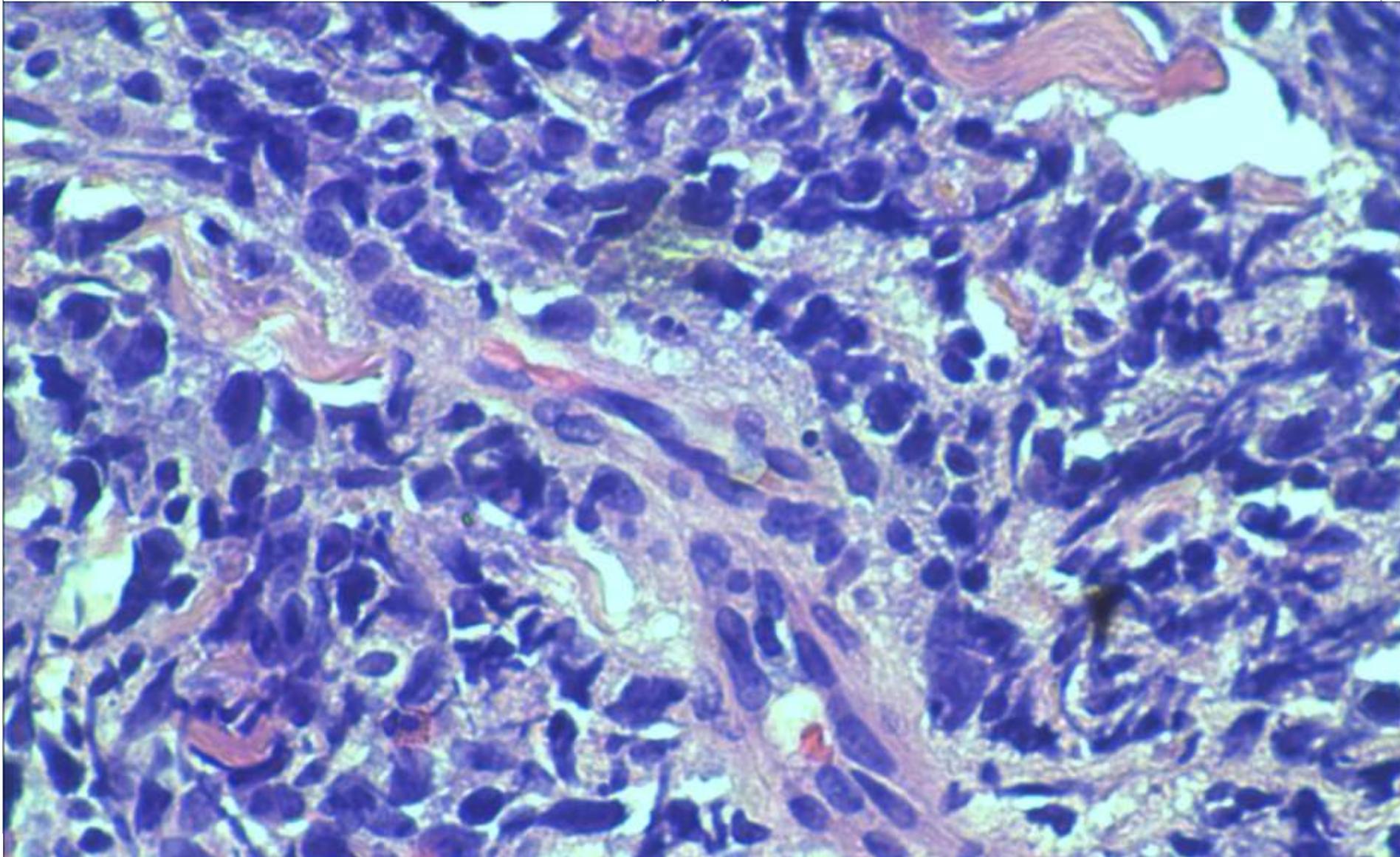
Diffuse FCCL



Primary Cut Follicle center cell, diffuse pattern



DLBC, LEG TYPE
>80 % CENTROBLASTS AND IMMUNOBLASTS



Cutaneous Pseudo-B & T cell lymphoma



- Pseudolymphoma-benign infiltrate that simulate cutaneous lymphoma histologically or clinically, some may harbor small clones by molecular test.
 - Synonyms: cutaneous lymphoid hyperplasia, lymphadenoma benigna cutis, lymphocytoma cutis, Spiegler-Fendt sarcoid
 - Classic division- Pseudo T and Pseudo-B
 - Pseudo-B more or less uniform in appearance with germinal center like reactions- Borrelia, L drug eruption, vaccine, tattoo, *infections- Syphilis, Herpes Zoster*
 - Pseudo- T are heterogeneous
 - ✦ With MF-like pattern- Actinic, contact dermatitis, L drug eruption, Lichenoid keratosis, L aureus, L sclerosis
 - ✦ With nodular pattern- CD30 pseudolymphomas, L drug eruption, arthropod bites

PSEUDOLYMPHOMAS 25% of cases



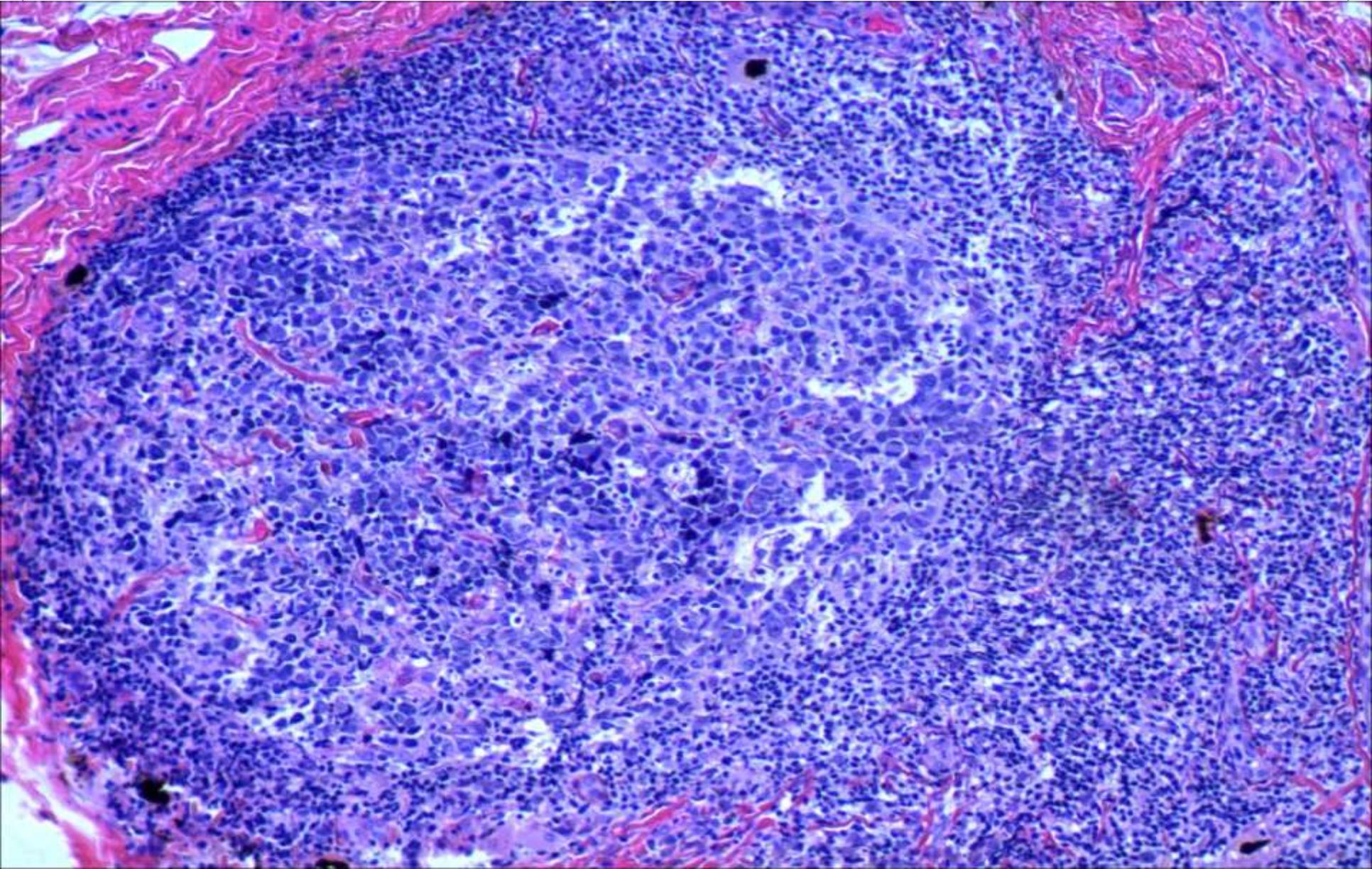
- **B CELL PSEUDOLYMPHOMA 3.8%**
 - ✦ **Germinal centers or > 70% nodules of B cells**
- **T CELL PSEUDOLYMPHOMA 9.0%**
 - ✦ **Band or nodular, >90% T cells**
- **MIXED B CELL AND T CELL PSEUDOLYMPHOMA 12.9%**
 - ✦ **Dermal nodules or perivascular, about equal number of B and T cells (40 to 60 %)**
- **CLONAL CLH 5.0%**
 - ✦ **Features of pseudolymphoma that has clonal T or B**

CD20 CD3 (with CD30)mixed phenotype

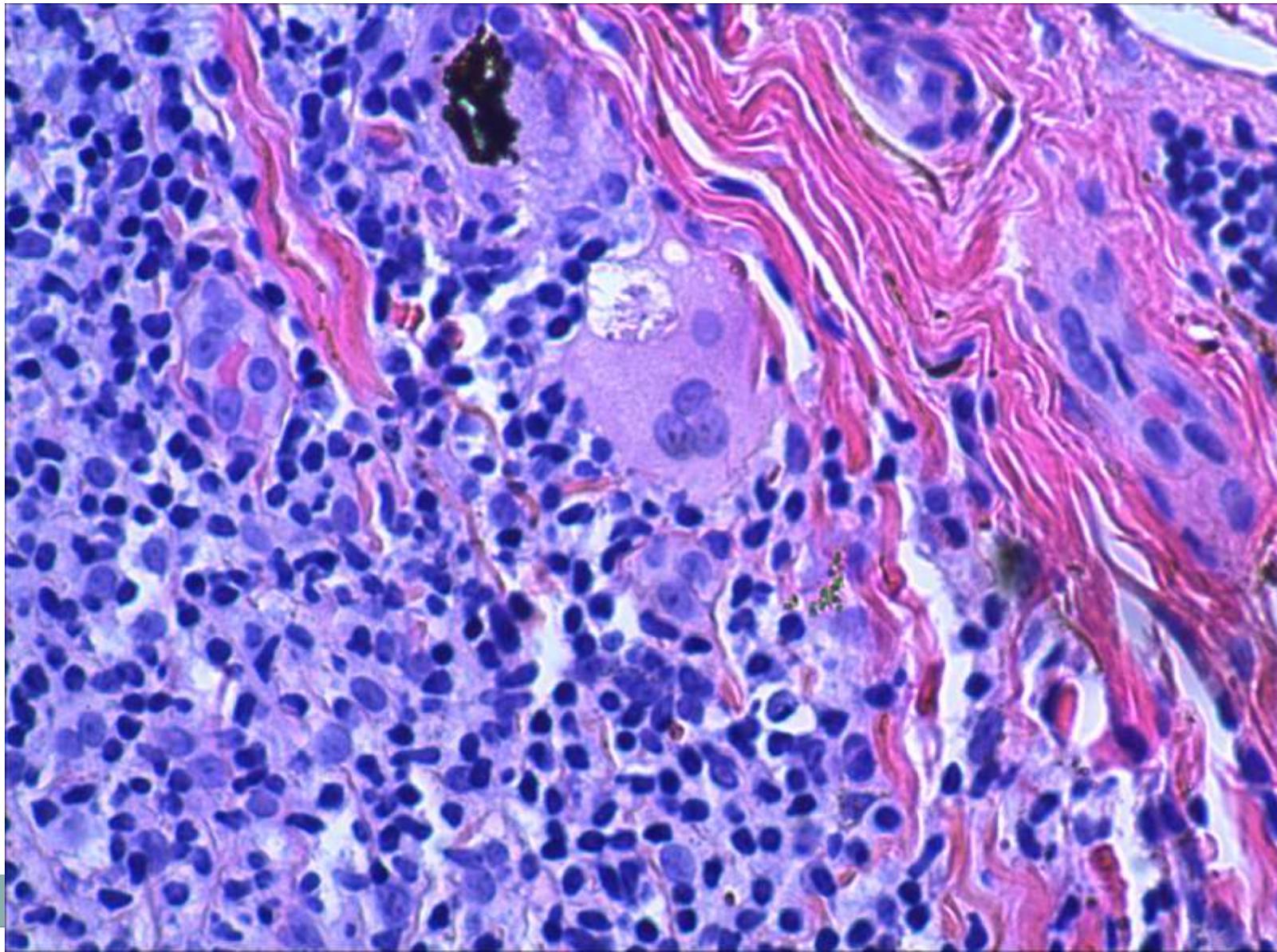


- **Cutaneous Mixed Pseudolymphoma 12.9%**
 - Majority unknown etiology
- **Clonal atypical Cutaneous Pseudolymphoma 5%**
 - Usually solitary, mostly in mixed pseudolymphoma category or one with exuberant granulomas, observed in patients with previous cutaneous B cell pseudolymphoma that recurred - now with atypical germinal centers, increased transformed cells, increased B: T cell ratio – Continuum REF: Kulow, Cualing et al.. Progression of cPseudoB to CBCL.
 - **Clonal Tumor of Uncertain Significance**
 - ✦ Similar to the terms: MGUS, MLUS, thyroid or prostate microcarcinomas, melanocytic lesions of uncertain significance

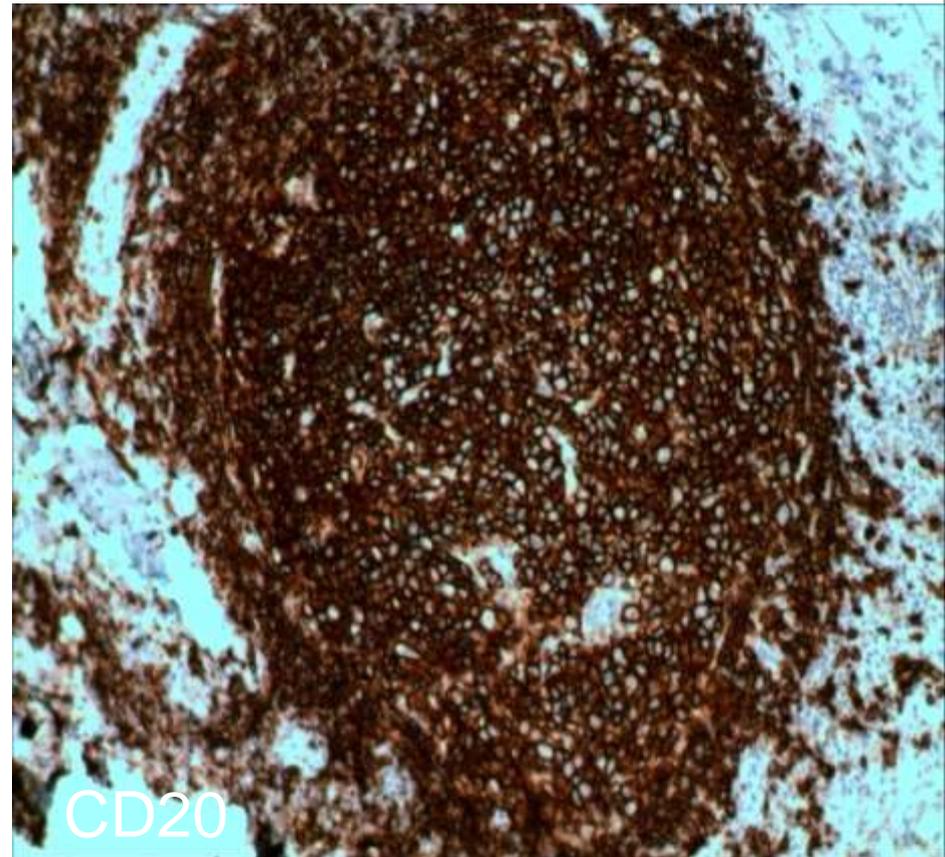
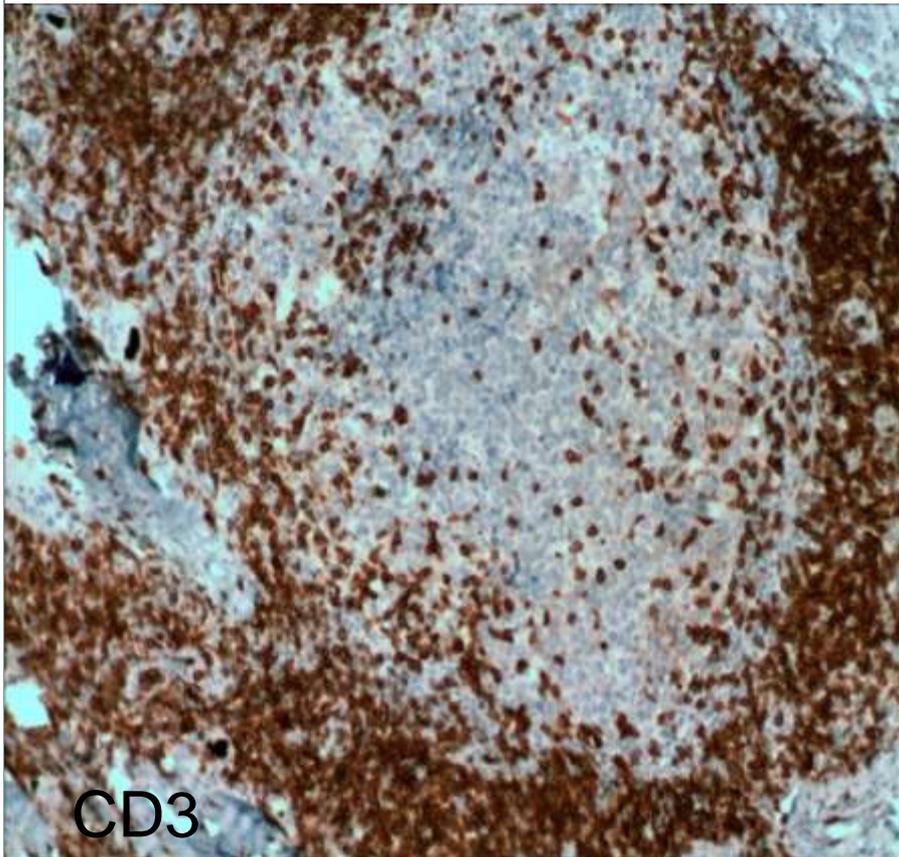
Cutaneous Lymphoid Hyperplasia or Pseudo- B cell lymphoma with defined etiology



CLH SECONDARY TO TATTOO PIGMENT



CLH SECONDARY TO TATTOO PIGMENT

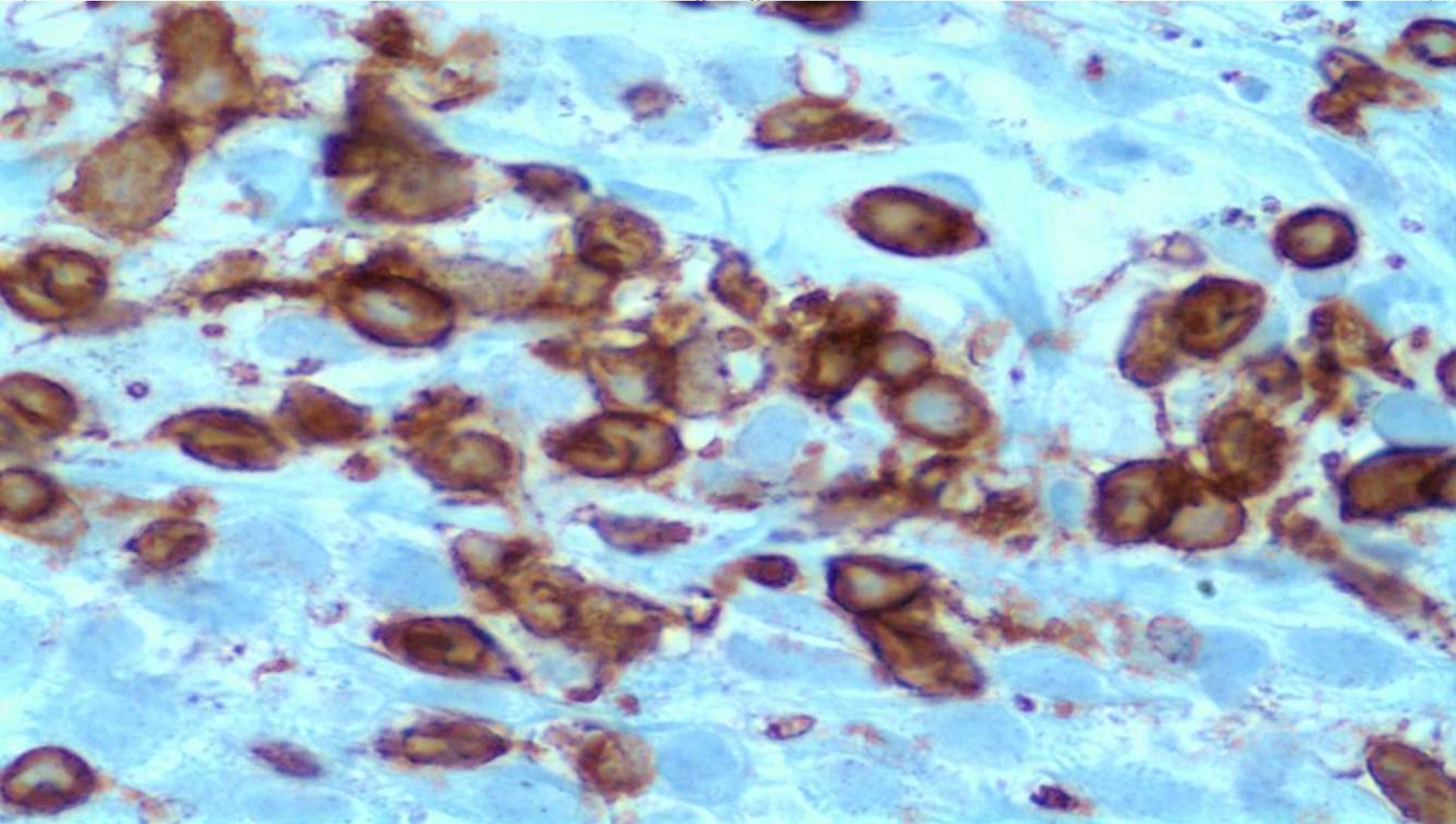


CD3 positive phenotype 27.8%



- **Cutaneous involvement by MF, PTCL 11.2 %**
 - Solitary Pleomorphic 3.8%
 - PTCL Unspecified 1.2%
 - Transformed MF 1.2%
 - CD8 ptcl, epidermotropic 1.2%
 - MF, Alibert Bazin type 3.8%
- **Pseudo T cell lymphoma 9%**
- **Lymphomatoid papulosis and CD30 Cutaneous Lymphomas 5.1%**
- **Intravascular cd30 T cell lymphoma 2.5%**

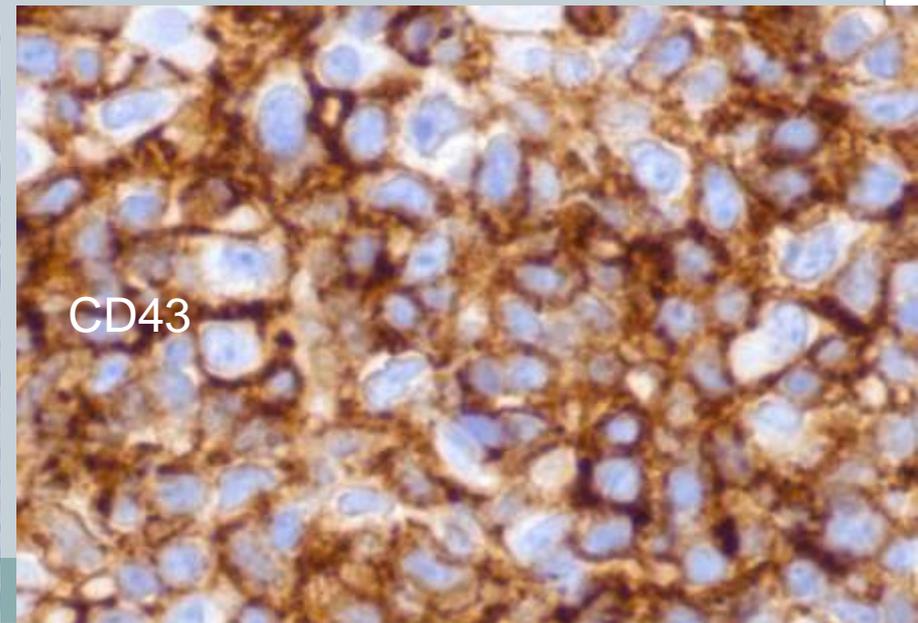
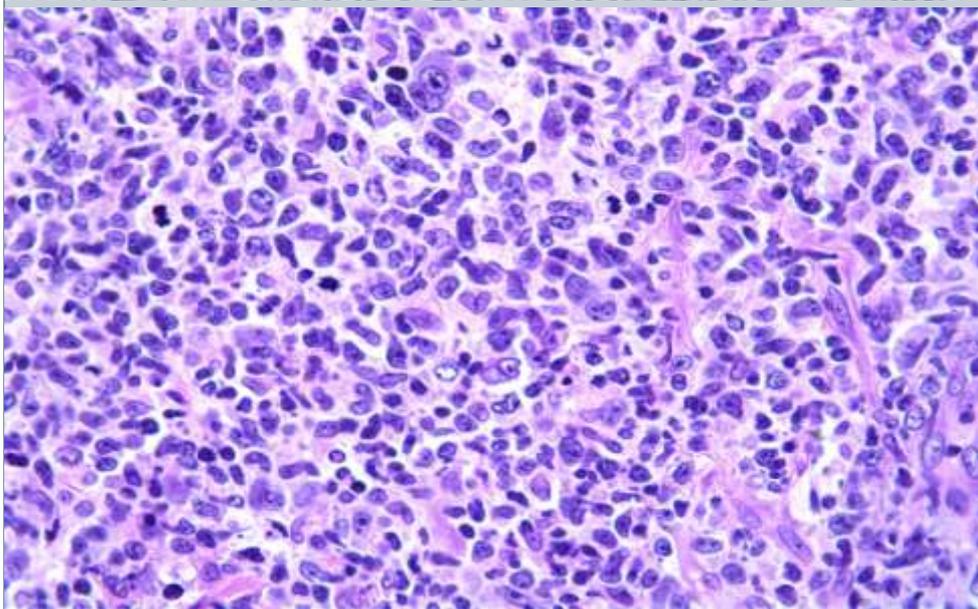
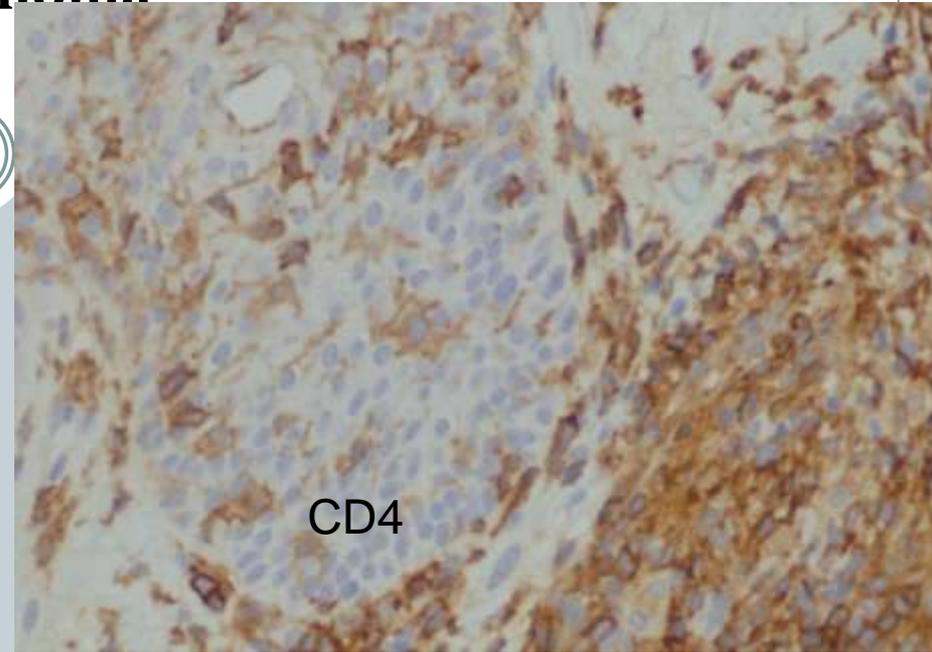
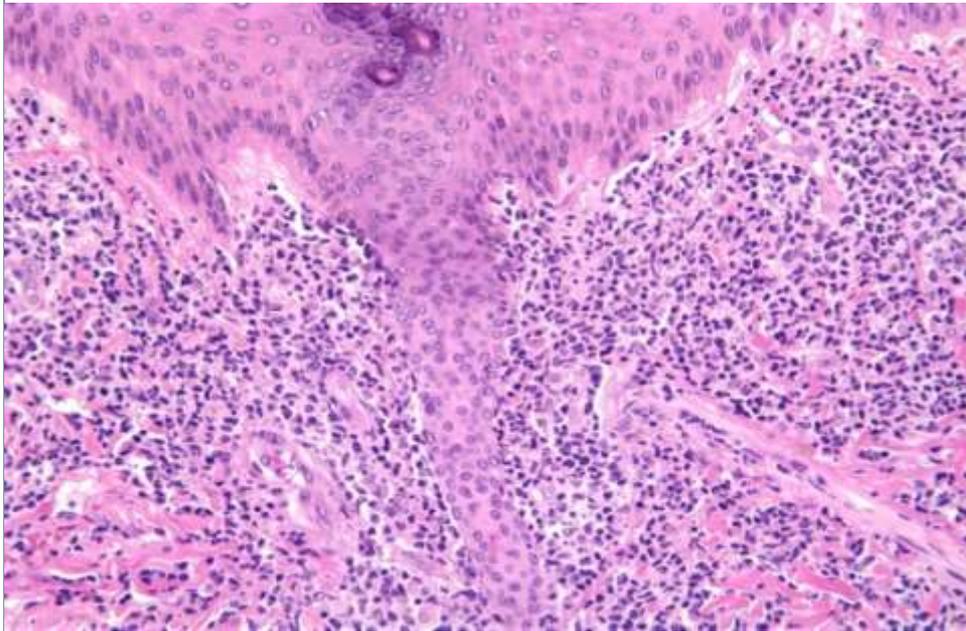
CD3 immunostain and vbeta clonal assay by flow cytometry



cCD4+pleomorphic T cell lymphoma



CD4+ lymphoma: CD4+ small/medium pleomorphic T cell lymphoma



CD30+ Lymphoproliferative Disorders

Primary cutaneous ALCL CD30+ large cell lymphoma

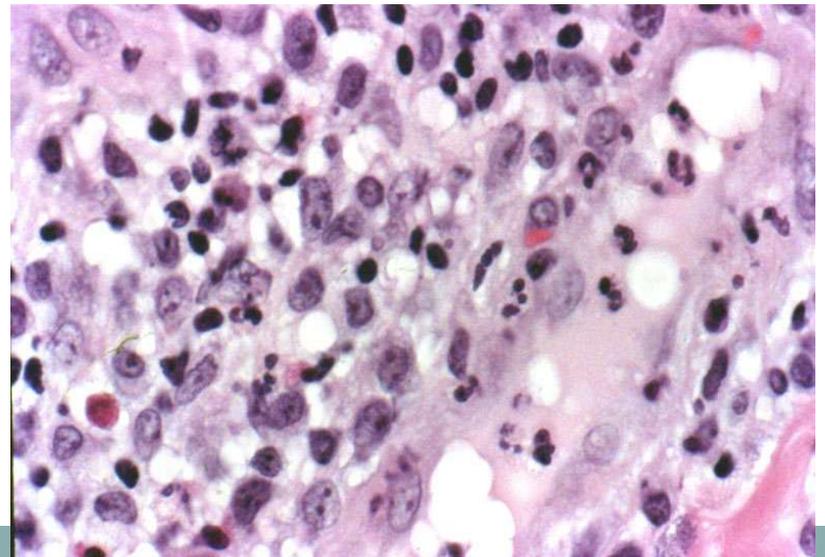
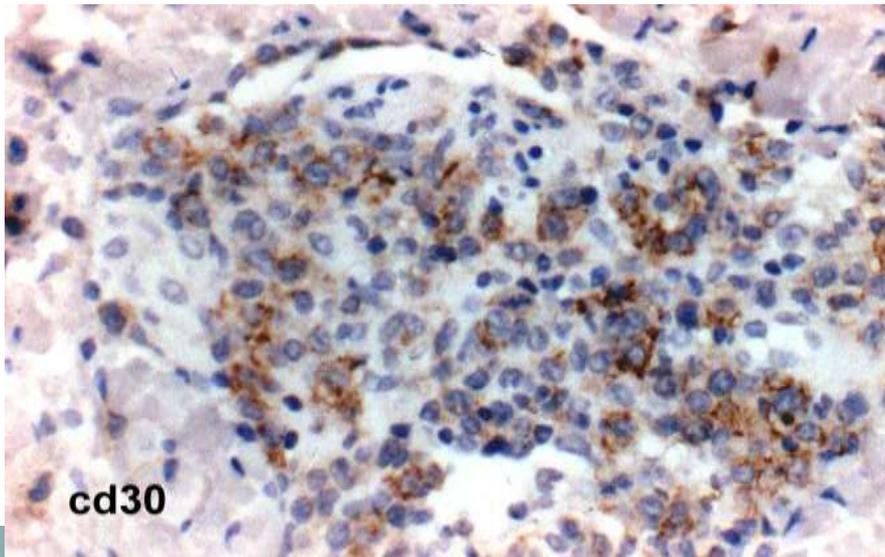
Lymphomatoid Papulosis histologic variants

Type A- RS-like with eos and neutrophils

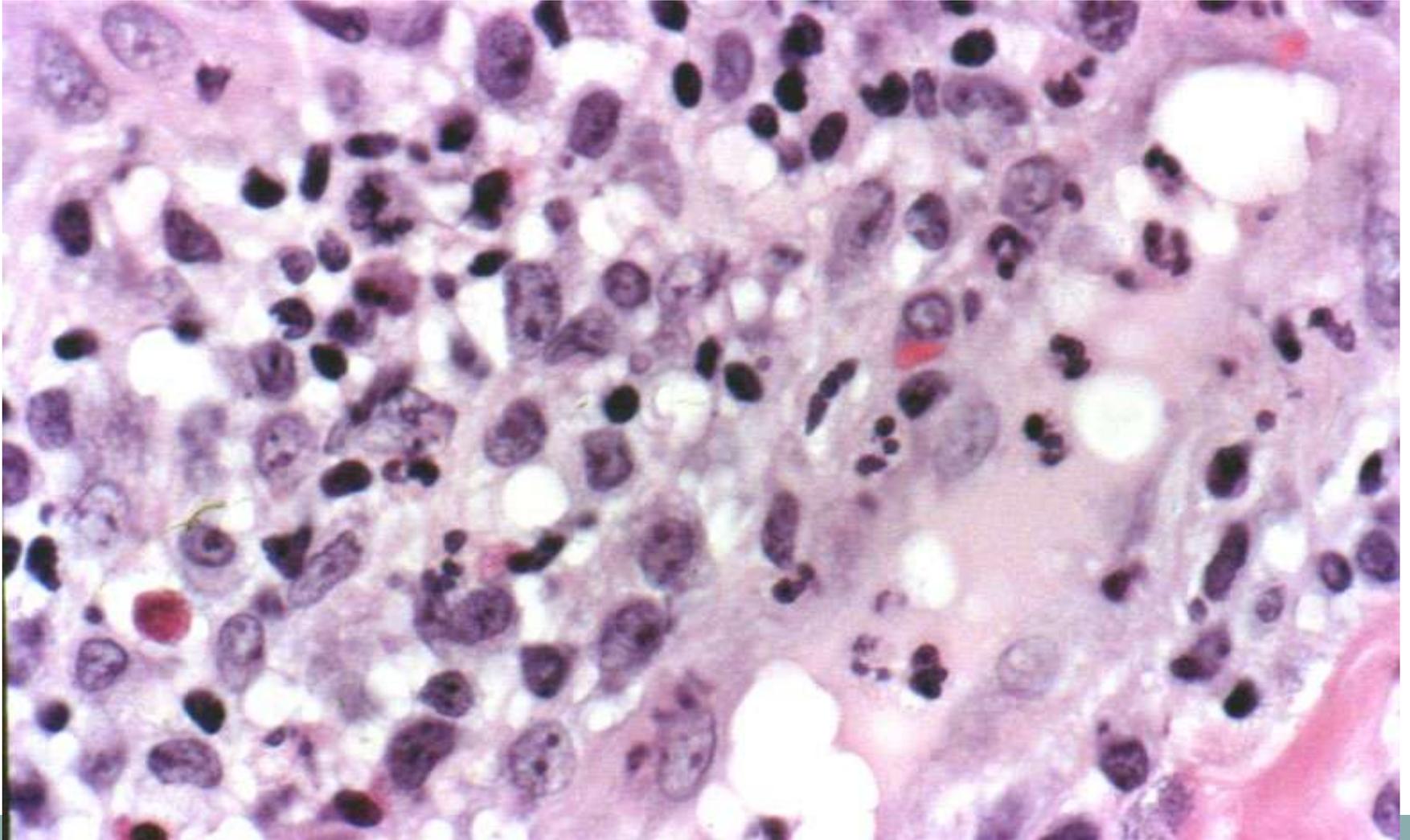
Type B- MF like with cerebriform cells

**Type C- borderline, monomorphic, dermal,
not in SQ, less inflammatory cells**

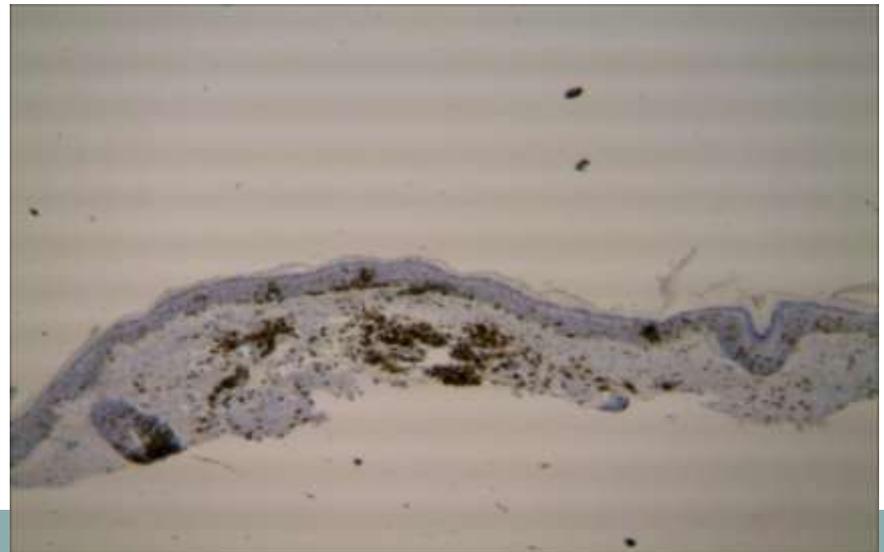
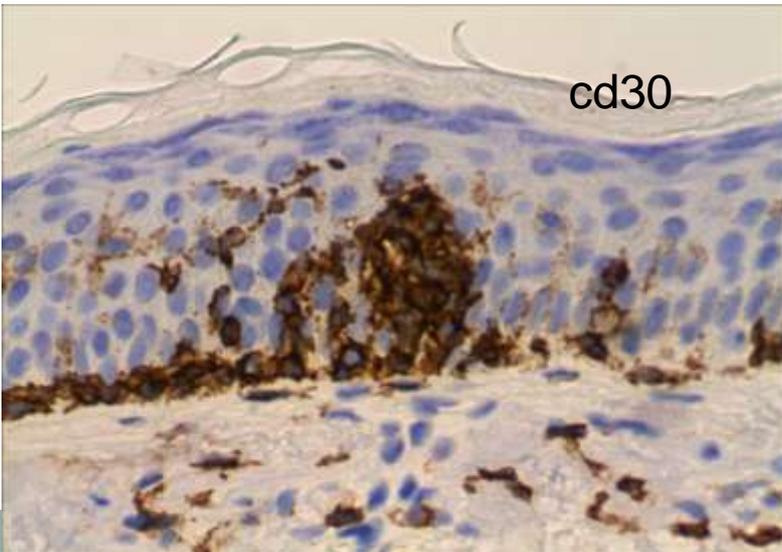
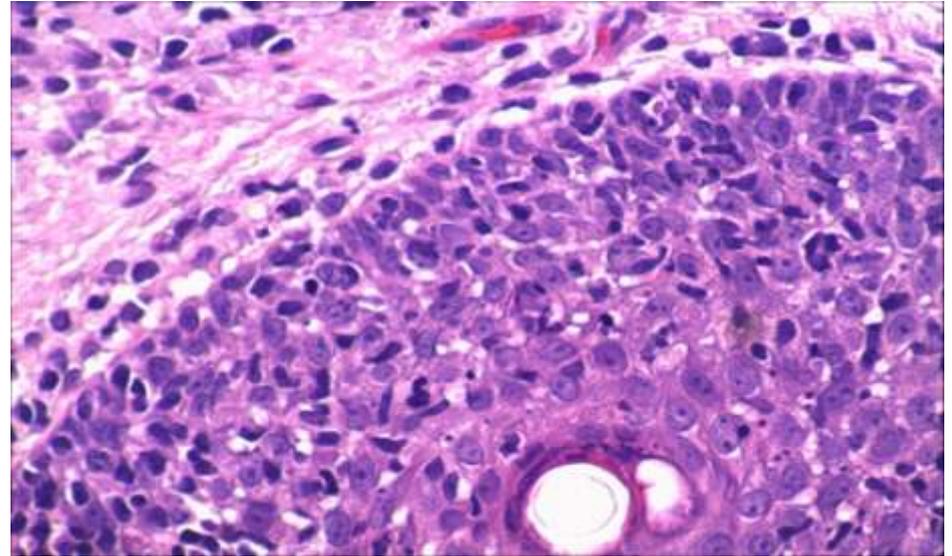
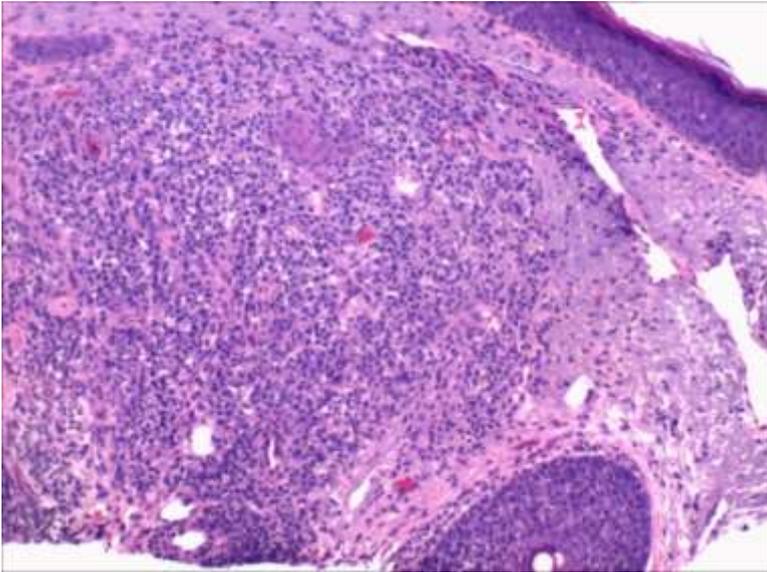
Lymphomatoid Papulosis(LyP)



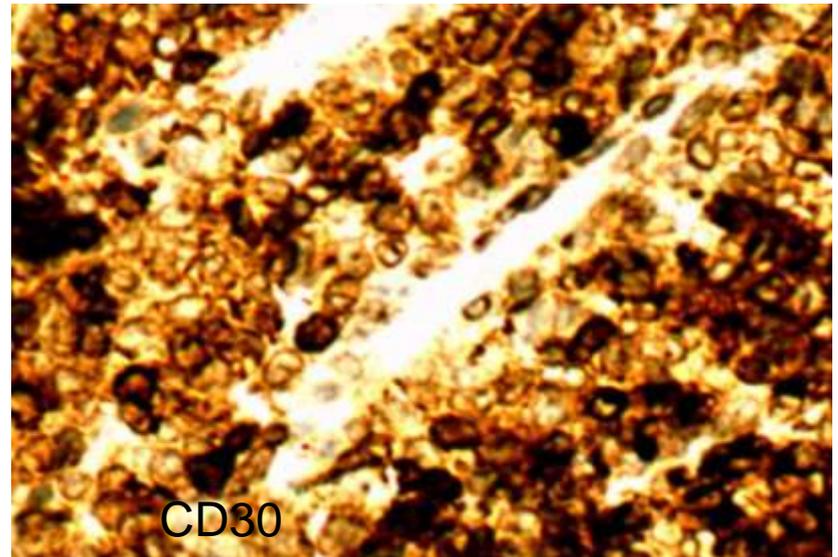
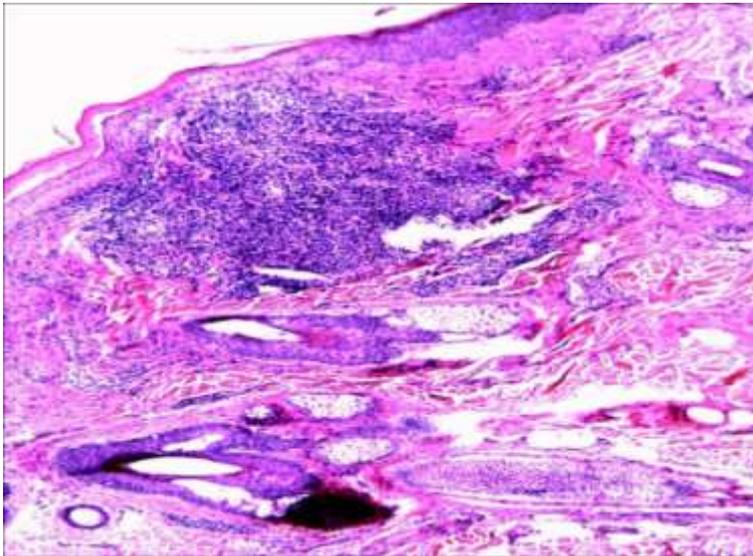
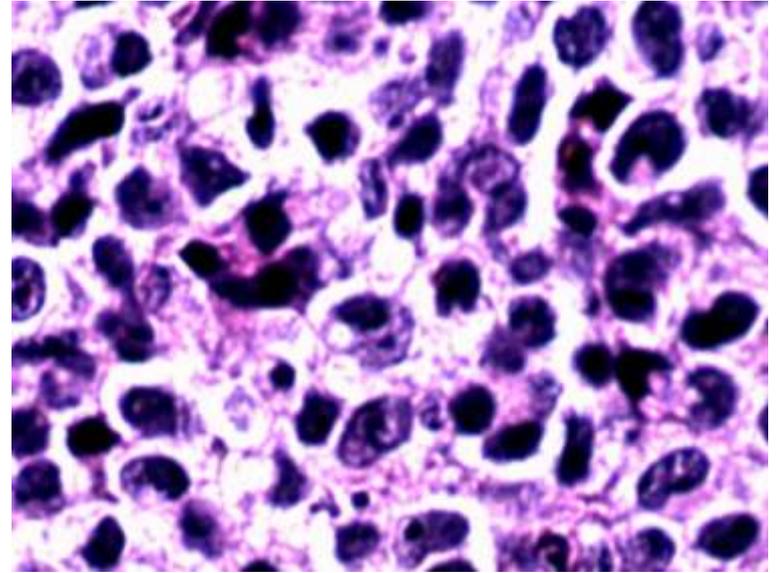
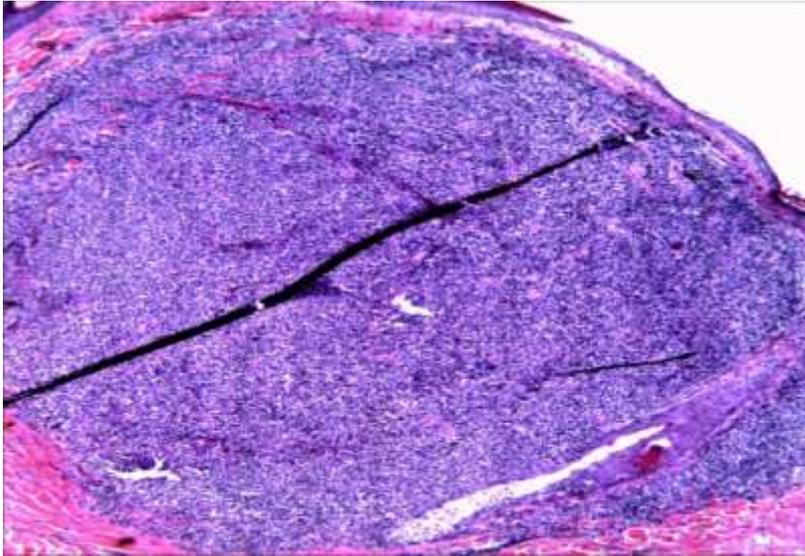
Lymphomatoid Papulosis(LyP type A)



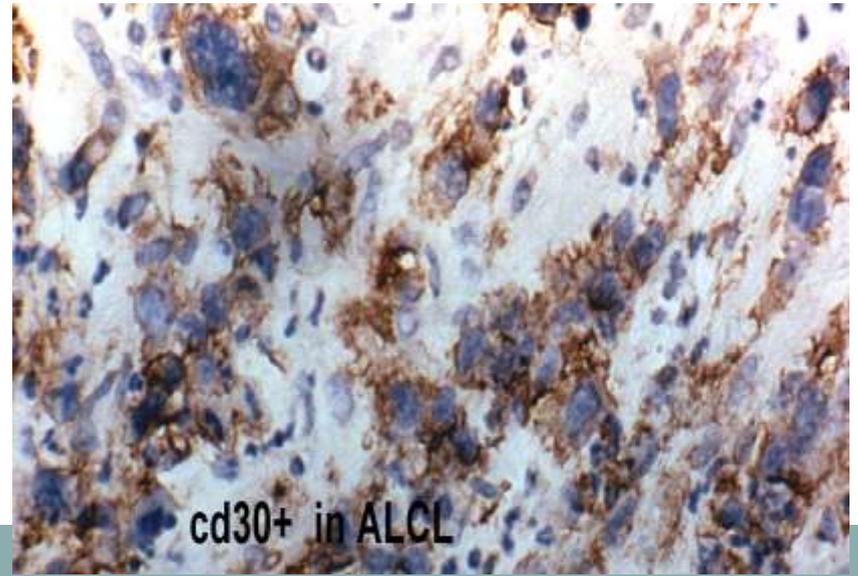
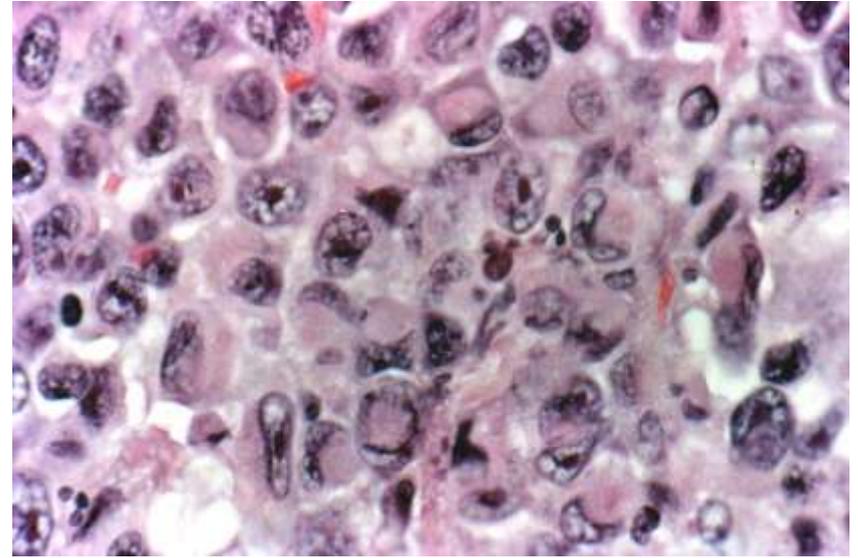
Lymphomatoid Papulosis (LyP type B)



Lymphomatoid Papulosis (LyP type C)



Primary Cutaneous Anaplastic lymphoma



- **In 1806, mycosis fungoides (MF) was first described¹**
 - **Alibert, a French dermatologist, described a severe disorder in which large necrotic tumors resembling mushrooms presented on a patient's skin**
- **In 1979, the term cutaneous T-cell lymphoma (CTCL) was proposed at an international workshop sponsored by the National Cancer Institute and as coined by the Lutzner group in 1975^{2,3}**
 - **CTCL was used to describe a heterogenous group of malignant T-cell lymphomas with primary manifestations in the skin**
 - **MF is the most common type of CTCL**
 - **Sézary syndrome (SS) is a variant of MF, occurring in about 5% of all cases of MF**



Baron Jean-Louis Alibert



¹Alibert JL. Description des Maladies de la Peau: Observées à l'Hospital St. Louis et Exposition des Meilleurs Methods Suivies pour leur Traitement. Paris. In: Barrois l'aîné et Fils, 1806.

²Lamberg SI, Bunn PA. *Cancer Treat Rep.* 1979;63:561 and Willemze R et al. *Blood* 1997;90:354-71.

³Lutzner, Edelson et al Cutaneous T cell lymphomas: The Sezary Syndrome, MF and related disorders, *Ann Int Med* 1975

WHO/EORTC Classification CTCLs

CTCL, NK-cell Lymphomas

MF/MF variants and subtypes

Folliculotropic MF not FM associated MF
Pagetoid reticulosis or solitary MF
Granulomatous MF not Granulomatous SS

Sézary syndrome

Adult T-cell leukemia/lymphoma

Primary cutaneous CD30+ lymphoproliferative disorders

Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis

Subcutaneous panniculitis-like T-cell lymphoma

Extranodal NK/T-cell lymphoma, nasal type

cutaneous peripheral T-cell lymphoma, unspecified

Primary cutaneous aggressive epidemotropic CD8+ T-cell lymphoma in WHO)
Cutaneous gamma/delta T-cell lymphoma (in WHO)
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell in WHO

Myelomonocytic blasts or PDC Neoplasm

WHO-EORTC 2005 Classification of Cutaneous T cell Lymphomas



CTCLs

5 year survival (%)

○ Indolent

- ✦ **MF** **88**
- ✦ **cALCL** **95**
- ✦ **LyP** **100**
- ✦ Subcut Panniculitis-like T cell lymphoma **82**
- ✦ cCD4+pleomorphic T cell lymphoma **75**

○ Aggressive

- ✦ **Sezary Syndrome** **24**
- ✦ NK/T cell lymphoma, nasal **NR**
- ✦ CD8+ T cell lymphoma **18**
- ✦ Gamma-Delta T cell lymphoma **NR**
- ✦ PTCL, unspecified **16**

Primary Cutaneous Lymphomas



- **75% of PCL are T-cell and 25% are B-cell lymphomas**
- **It is important to distinguish between systemic lymphomas and PCL.**
- **Except MF, number of primary Cutaneous PTCLs have worse prognosis than the nodal types.**
 - In contrast, Cutaneous B cell lymphomas have a much better prognosis than the nodal lymphoma that looks morphologically identical.
 - Pseudolymphomas may be part of continuum

Diagnostic Approach



The diagnosis in CL is established by the combination of **CHIP**:

- **C**linical features
- **H**istopathology
- **I**mmunophenotypic
- **P**robes for molecular