Indolent T (and NK)-cell Lymphoproliferative Disorders (LPD)

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Tumour-like lesions with T lymphocytic predominance

Kikuchi disease
Indolent T-lymphoblastic proliferation
Autoimmune lymphoproliferative syndrome

Precursor T-cell neoplasms

T acute lymphoblastic leukaemia / lymphoma
- T acute lymphoblastic leukemia / lymphoma, NOS
- Early T precursor acute lymphoblastic leukaemia / lymphoma

Mature T-cell neoplasms

Mature T-cell leukemias
- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia **
- Adult T-cell leukaemia/lymphoma
- Sezary syndrome

Primary cutaneous T-cell neoplasms
- Primary cutaneous CD4+ small or medium T-cell LPD
- Mycosis fungoides **
- Lymphomatoid papulosis **
- Primary cutaneous anaplastic large cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Primary cutaneous gamma/delta T-cell lymphoma
- Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma (provisional)
- Primary cutaneous acral CD8-positive T-cell lymphoma
- Primary cutaneous T-cell lymphoma, NOS

Intestinal T-cell neoplasms and lymphoproliferative disorders
- Indolent T-cell LPD of the gastrointestinal tract
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Intestinal T-cell lymphoma, NOS

Hepatosplenic T-cell lymphoma
- Hepatosplenic T-cell lymphoma

Anaplastic large cell lymphoma
- Anaplastic large cell lymphoma, ALK positive
- Anaplastic large cell lymphoma ALK negative (DUSP22/TP63/NOS)
- Anaplastic large cell lymphoma, breast implant-associated

Peripheral T-cell lymphoma with TFH phenotype
- Follicular T-cell lymphoma
- Angioimmunoblastic T-cell lymphoma
- Peripheral T-cell lymphoma with TFH phenotype

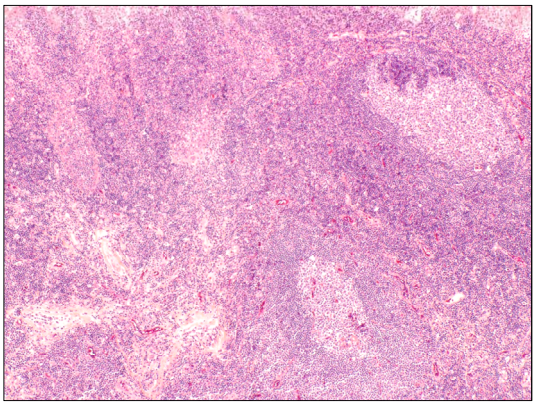
Peripheral T-cell lymphoma
- Peripheral T-cell lymphoma, NOS
- EBV-positive nodal T-cell lymphoma

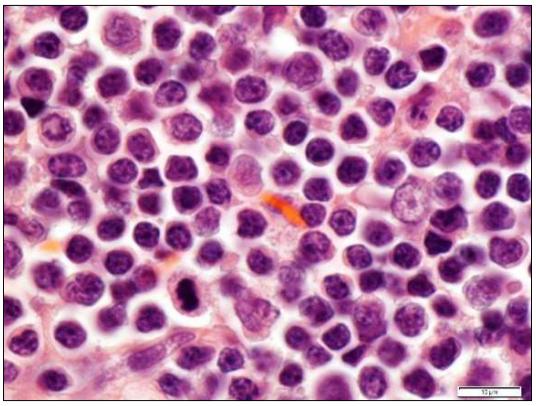
EBV-positive lymphoproliferative diseases of childhood
- Severe mosquito bite allergy
- Hydroa vacciniforme-like lymphoproliferative disorder
- Chronic active EBV infection of T- and NK-cell type, ** systemic form
- Systemic EBV+ T-cell lymphoma of childhood

From : https://whobluebooks.iarc.who.int/structures/haematolymphoid/

Indolent T lymphoblastic proliferation

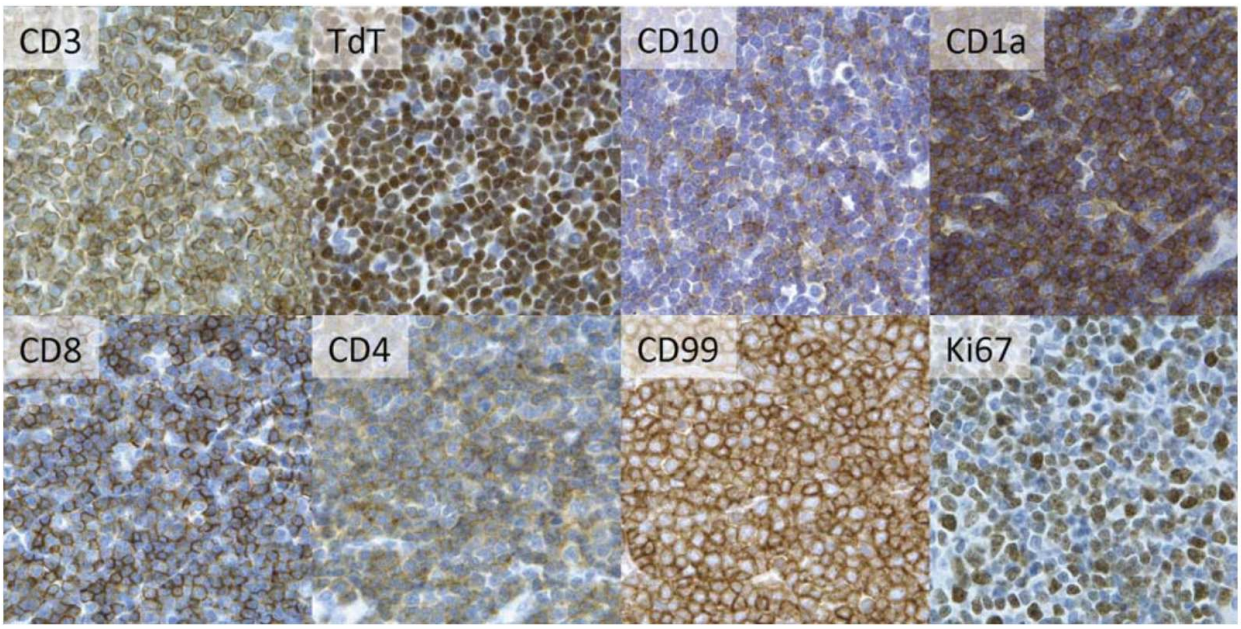
Case credit : Amy Duffield, M.D., Ph.D.

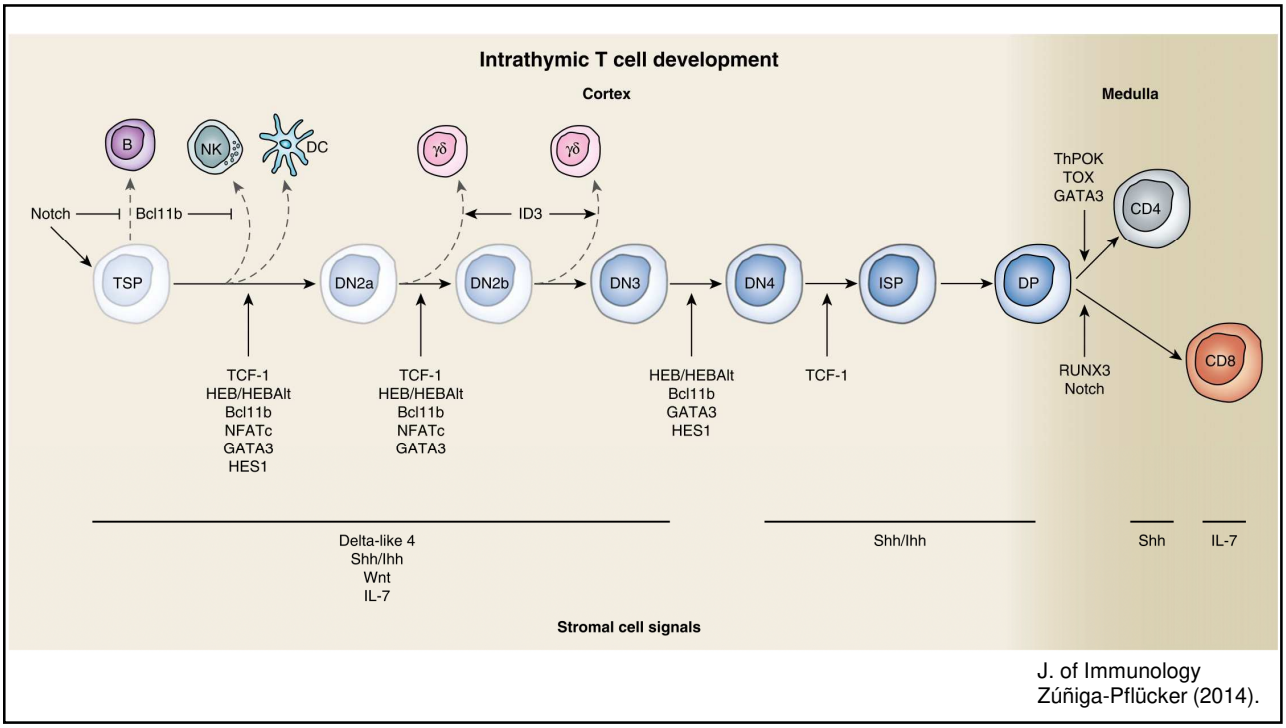




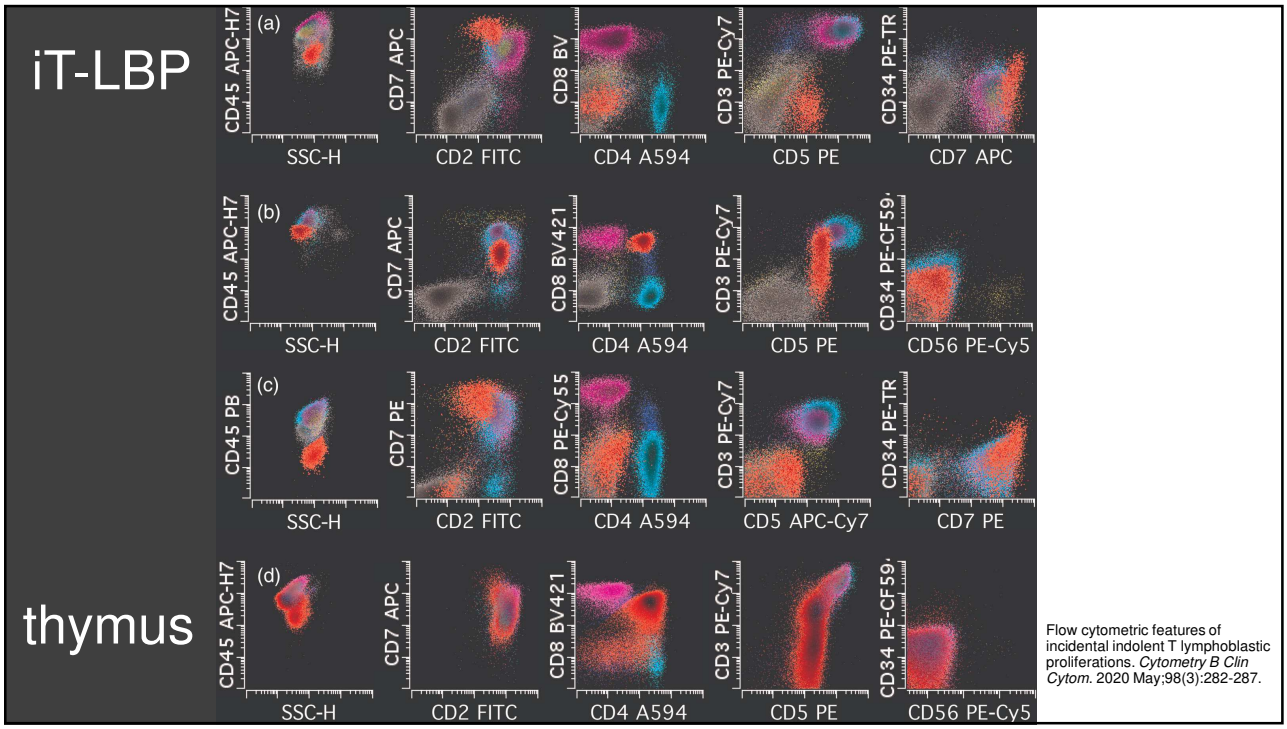
Indolent T-Lymphoblastic Proliferation (iT-LBP): A Review of Clinical and Pathologic Features and Distinction from Malignant T-Lymphoblastic Lymphoma

Robert S. Ohgami, MD, PhD, Daniel A. Arber, MD, James L. Zehnder, MD, Yasodha Natkunam, MD, PhD, and Roger A. Warnke, MD





J. of Immunology
Zúñiga-Pflücker (2014).



Flow cytometric features of incidental indolent T lymphoblastic proliferations. *Cytometry B Clin Cytom.* 2020 May;98(3):282-287.

indolent T lymphoblastic proliferations (iT-LBP) *vs.* thymus or thymoma

Anatomic location favoring thymus :

- Cervical extension of the thymus is normal in kids & can be seen in adults
- Thymic precursor descends from 3rd/4th pharyngeal pouches into the mediastinum in fetal life; residual thymic tissue can be seen along the path of descent

Architecture favoring thymus :

- Hassall's corpuscles (not metastatic squamous cell carcinoma)

Architecture favoring iT-LBP :

- Lymph node +/- germinal centers with features of Castleman's disease
- Absence of cytokeratins marking normal thymic epithelium

indolent T lymphoblastic proliferations (iT-LBP)
vs.
T acute lymphoblastic leukemia / lymphoma (T-LBL)

Molecular studies :

- Clonal in T-LBL (if not immature CD4-/CD8- phenotype)
- Polyclonal in iT-LBP

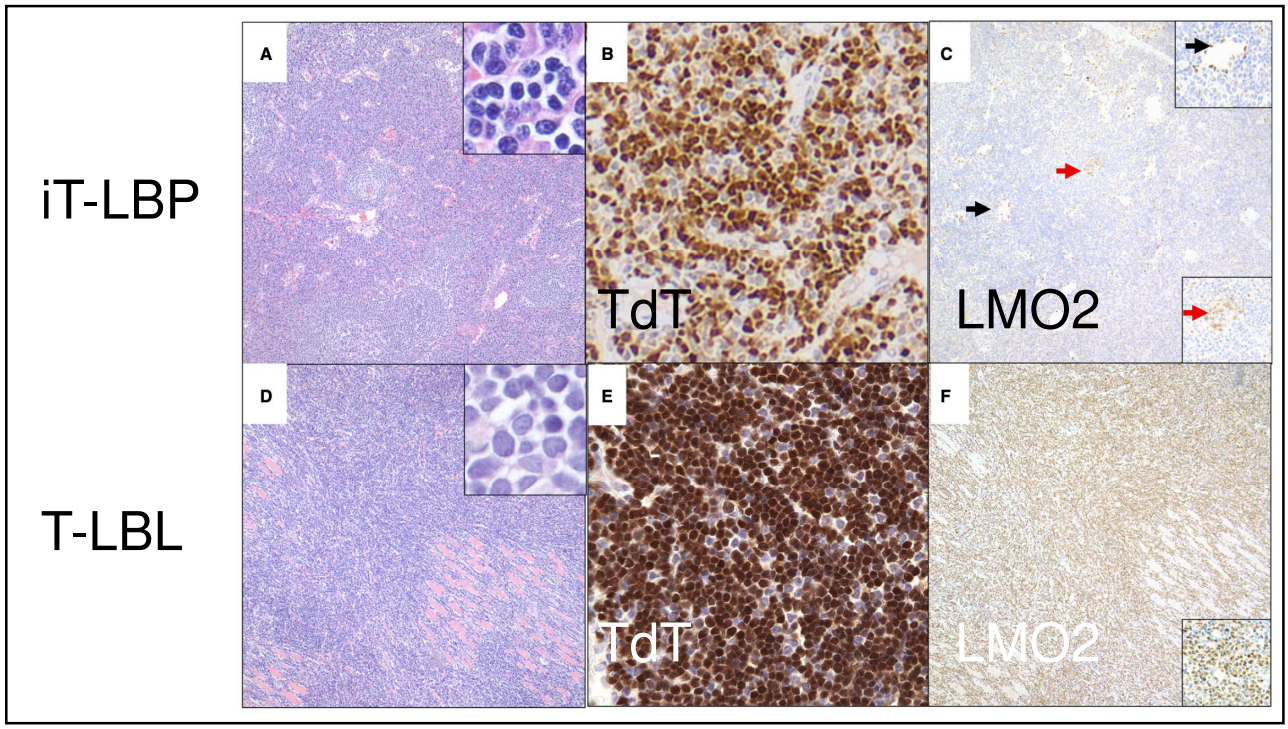
Immunophenotype :

- Abnormal, monotonous population in T-LBL
- Normal population (reminiscent of maturing thymocytes) in iT-LBP
- LMO2 expression in T-LBL

Histopathology 2020, **77**, 984–988. DOI: 10.1111/his.14176

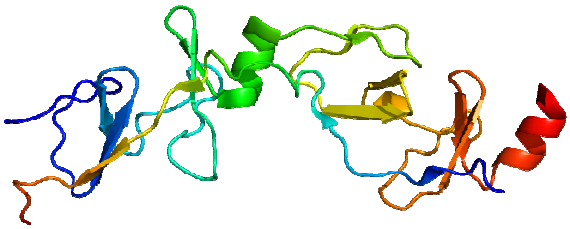
LIM domain only 2 (LMO2) expression distinguishes T-lymphoblastic leukemia/lymphoma from indolent T-lymphoblastic proliferations

Nivaz Brar,[1] Alexandra Butzmann,[2] Jyoti Kumar,[3] Raheem Peerani,[3] Elizabeth A Morgan,[4] George Grigoriadis,[5] Beena Kumar,[5] R Maciej Tatarczuch,[5] Roger A Warnke[3] & Robert S Ohgami[2]



LMO2

LIM domain only 2 (rhombotin-like 1),
LMO2, RBTNL1, RBTN2, RHOM2, LIM Domain Only Protein 2, TTG2,
and T-Cell Translocation Protein 2



LMO2 encodes a cysteine-rich, two LIM domain protein that interacts with TFs in hematopoietic lineages.

Many mechanisms of upregulation in ALL / LBL:

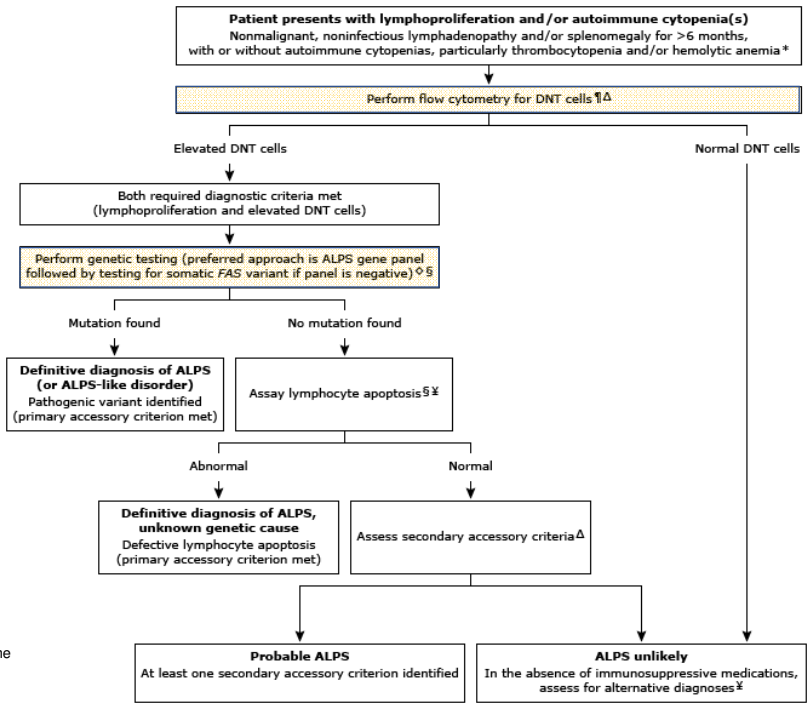
- proximity to T-cell translocation cluster (11p13 ttc);
- mutations in an upstream noncoding DNA element to form an enhancer;
- mutations of LMO2 intron 1.

ALPS -
Autoimmune lymphoproliferative syndrome

Typical presentation is in children with LAD, +/- splenomegaly
Expansions of double negative (TCR αβ+, CD4–, CD8–) T cells

Autoimmune cytopenias, (later) lymphomas (usually HL, DLBCL)

Germline Fas cell surface death receptor (*FAS*) gene mutations result in a failure of cells to undergo apoptosis.



Up To Date
Autoimmune lymphoproliferative syndrome (ALPS): Clinical features and diagnosis
Author: Jack JH Bleesing, MD, PhD

expansions of T-large granular lymphocytes (T-LGL)

T-LGLs usually express CD3+, TCR αβ+, CD4–, CD5dim, CD8+, CD16+, CD27–, CD28–, and CD57+ phenotype

vs.

T-cell LGL leukemia

> 6mo. elevated T cells, usually > 2-20x10^9/L
1/3 of cases have *STAT3* SH2 domain activating mutations
(rarely *STAT5B*, may behave more aggressively)
as a rule, have clonal TCR rearrangements

expansions of NK-LGLs

NK-LGLs are characterized by CD2+/sCD3-/CD3ε+/TCRαβ-/CD4-/CD8+/CD16+/CD56+ phenotype

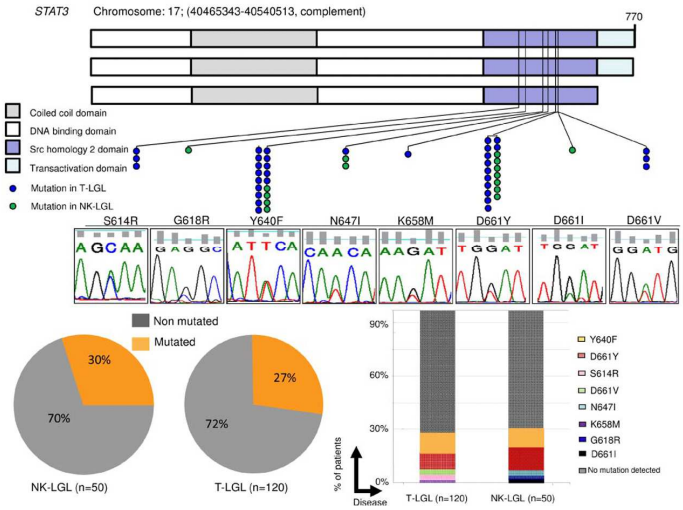
vs.

chronic LPD of NK cells

> 6mo. elevated NK cells, usually > 2x10^9/L
provisional entity in 2017 WHO
1/3 of cases have *STAT3* SH2 domain activating mutations

STAT3 mutations unify the pathogenesis of chronic lymphoproliferative disorders of NK cells and T-cell large granular lymphocyte leukemia

Andres Jerez,[1] Michael J. Clemente,[1] Hideki Makishima,[1] Hanna Koskela,[2] Francis LeBlanc,[3] Kwok Peng Ng,[1] Thomas Olson,[3] Bartlomiej Przychodzen,[1] Manuel Afable,[1] Ines Gomez-Segui,[1] Kathryn Guinta,[1] Lisa Durkin,[4] Eric D. Hsi,[4] Kathy McGraw,[5] Dan Zhang,[3] Marcin W. Wlodarski,[6] Kimmo Porkka,[2] Mikkael A. Sekeres,[1] Alan List,[5] Satu Mustjoki,[2] Thomas P. Loughran,[3] and Jaroslaw P. Maciejewski[1]

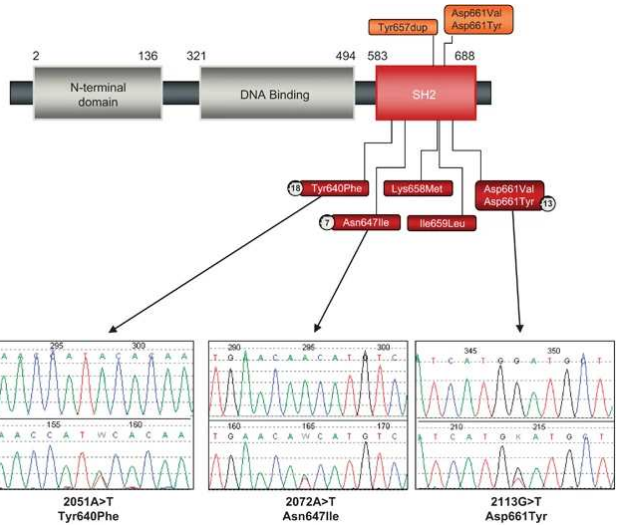


STAT3 mutations are highly specific for large granular lymphocytic leukemia

Leukemia (2013) **27**, 1598–1600; doi:10.1038/leu.2012.350

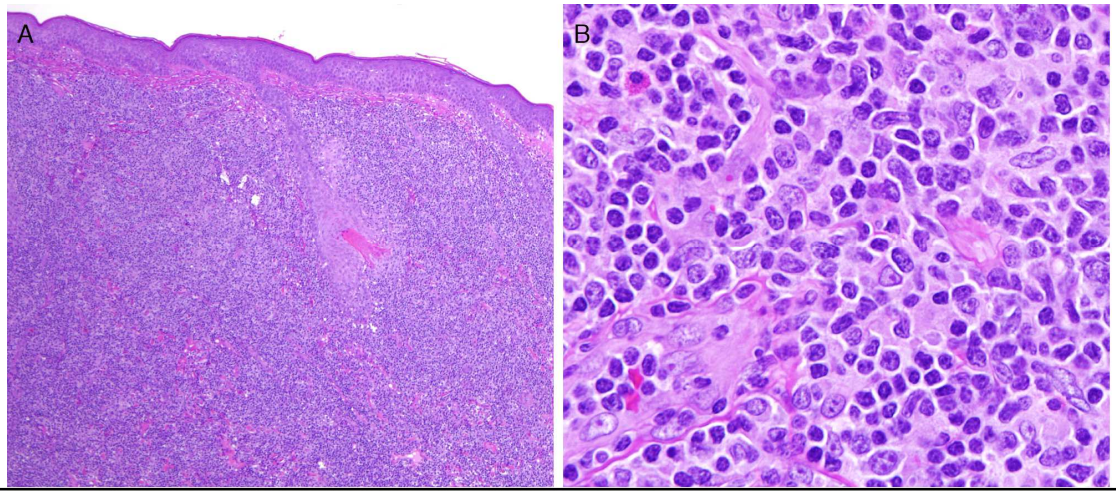
Large granular lymphocytic (LGL) leukemia is a rare lymphoproliferative disorder characterized by the presence of increased numbers of LGL cells in the peripheral blood.[1] According to the World Health Organization (WHO) classification, LGL leukemia can be divided into the two morphologically similar subtypes of T-cell LGL leukemia and chronic natural killer (NK)-cell lymphoproliferative disorder (CLPD-NK).[1] Although derived from distinct cell lineages, the clinical presentation is very similar and dominated by recurrent infections associated with neutropenia, anemia, splenomegaly and autoimmune diseases, particularly rheumatoid arthritis.[2] Molecular diagnostics of these diseases thus far was limited to the analysis of T-cell receptor (TCR) rearrangements for evaluation of T-cell clonality. Very recently, somatic *STAT3* mutations have been described with a high frequency of 40% in T-LGL leukemia[3] and 30% in CLPD-NK.[4] The discovery of *STAT3* mutations in T-LGL leukemia reveals a significant diagnostic value as it allows with high specificity to distinguish many cases of LGL leukemia from other mature T-cell neoplasms and reactive conditions. Thus, it strongly supports immunophenotyping and morphology in diagnostics of T-LGL leukemia and CLPD-NK. All mutations were found to be located in the Src homology 2 (SH2) domain, which mediates the dimerization and activation of the STAT protein.[3,4] The aim of our study was to further analyze the frequency and potential prognostic impact of *STAT3* mutations in patients with T-LGL leukemia in comparison with cases with other T-cell malignancies

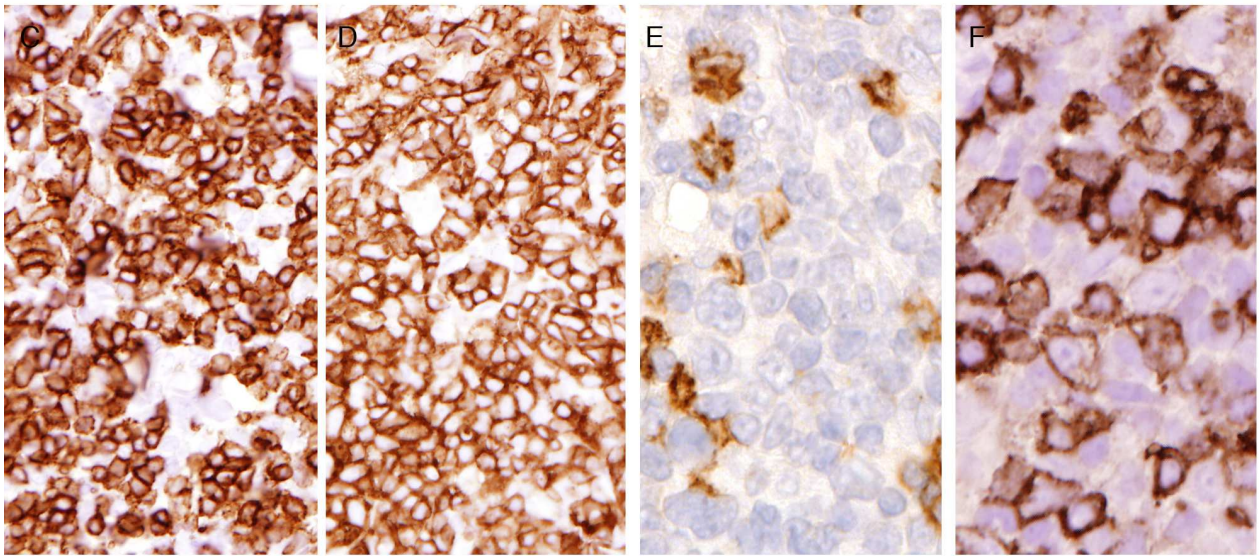
Munich Leukemia Laboratory and adhered
Declaration of Helsinki. Cytomorphological as
on May–Grünwald–Giemsa stains. Immu
performed in 43/55 cases according to the
procedures.[5] The antigens analyzed includ
CD4, CD5, CD7, CD8, CD34, CD56, CD57, TCR
antibodies were purchased from Immunotec
Screening for *STAT3* mutations was perform
sequencing of the SH2 domain that is enc
previously described.[3] TCR rearrangements
multiplex PCR with subsequent fragment an
variables were compared between differer
χ^2-test and continuous variables by Student'
considered significant at $P<0.05$. All the r
two-sided. No adjustments for multiple
performed. SPSS version 19.0 (IBM Corpo
USA) was used for statistical analysis. Ov
leukemia cases (72.7%), 41 *STAT3* mutation
mutations were missense mutations. Six diffe
observed (Figure 1). Tyr640Phe ($n=18$) and
accounted for 75.6% of all mutations de
harbored two mutations (Asn647Ile and T
detected a Ile659Leu in one patient, which ha
previously.[3,4] There was no association of S
age, sex and peripheral blood counts in T
(Table 1). Cases with *STAT3* mutations had a s
CD3 (percentage positive cells, 76 ± 20% vs
and TCRαβ (68 ± 19% vs 48 ± 20%, $P=0.0$
explained by the significantly elevated c



Primary cutaneous CD4+ small/medium T-cell LPD

Case credit : Wenbin Xiao, M.D., Ph.D.



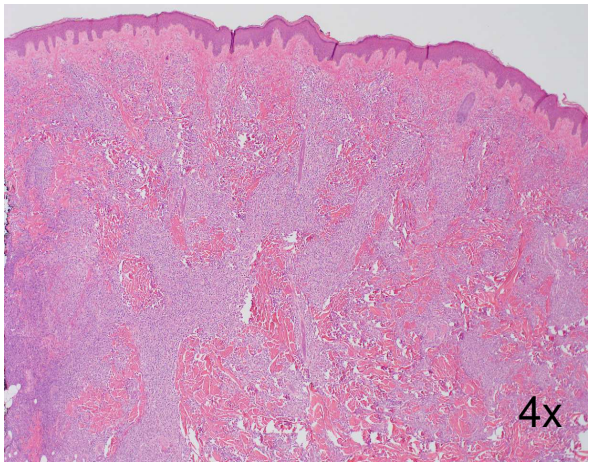


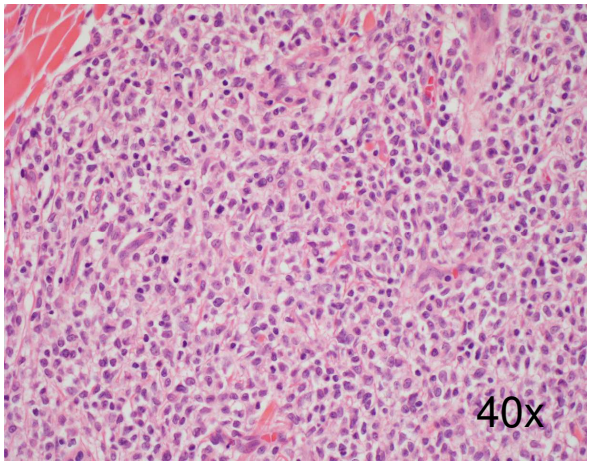
Primary cutaneous CD4+ small/medium T-cell LPD

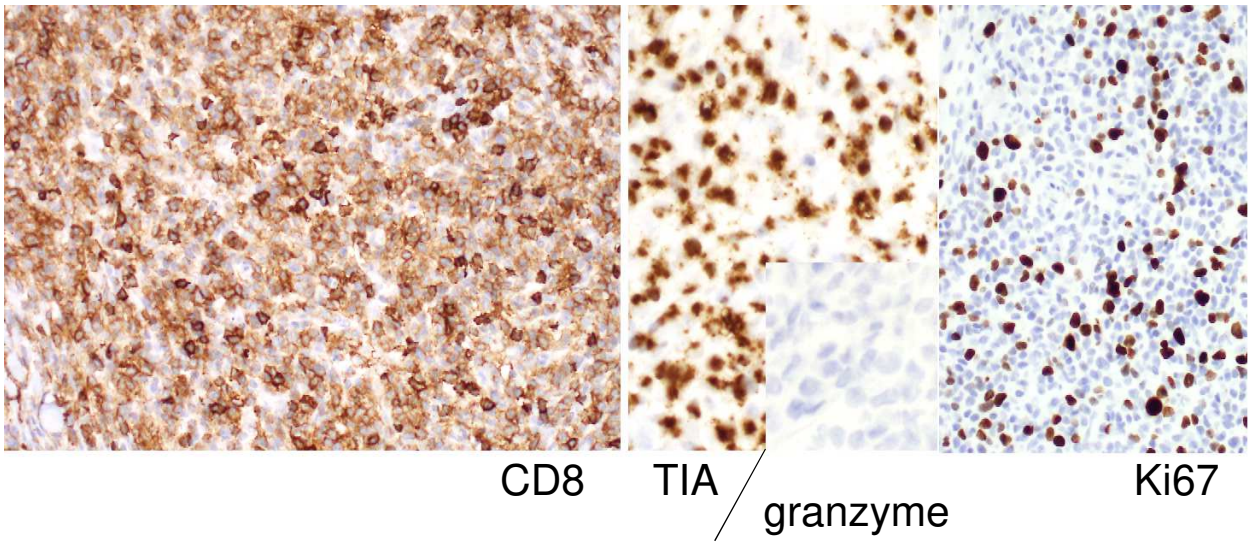
- typically a solitary plaque or nodule
- T cell phenotype, CD7+/-, low Ki67 (5%), CD4+ by definition, CD8-negative, CD30-negative
- PD-L1, BCL6, CXCL13 suggest a T follicular helper phenotype
- EBER negative
- TCR clonal
- Respond to steroids, excision; spontaneous remission after biopsy; infrequent local recurrence

Primary cutaneous acral CD8+ T-cell lymphoma

Case credit : Wenbin Xiao, M.D., Ph.D.





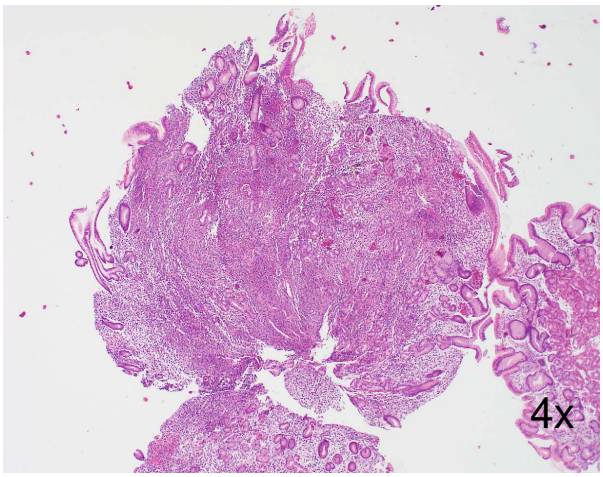


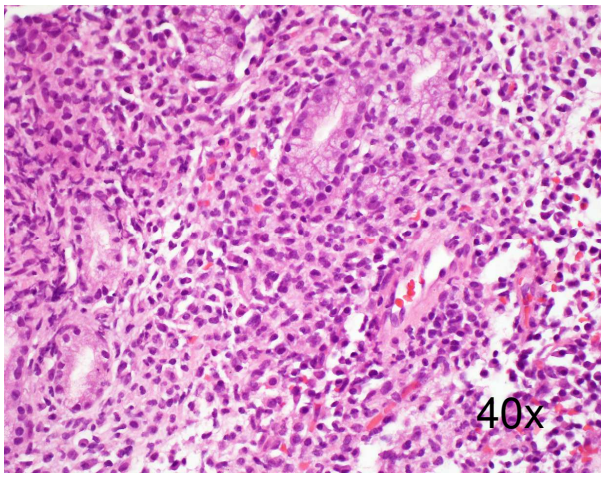
Primary cutaneous acral CD8+ T-cell lymphoma

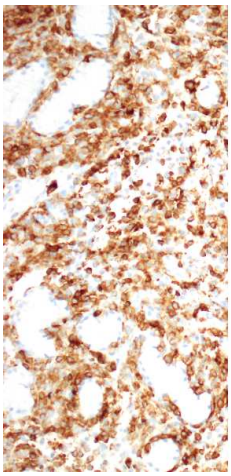
- typically a solitary nodule distal aspects of the head (ears, nose) and the extremities (hands, fingers, feet, toes)
- T cell phenotype, CD7+/-, low Ki67 (10%), CD8+ by definition
- CD56, CD57 and CD30 negative
- EBER negative
- TCR clonal
- Respond to excision; radiotherapy

Indolent T-cell and NK-cell LPD of the GI tract

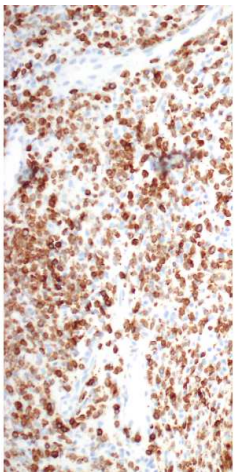
Case credit : Wenbin Xiao, M.D., Ph.D.



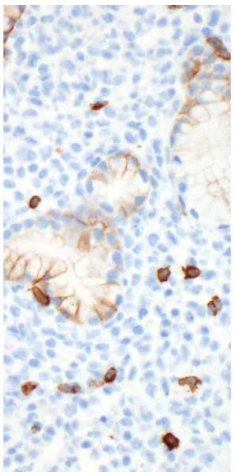




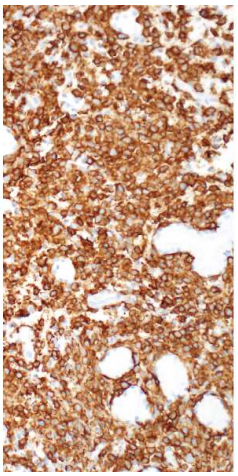
CD2



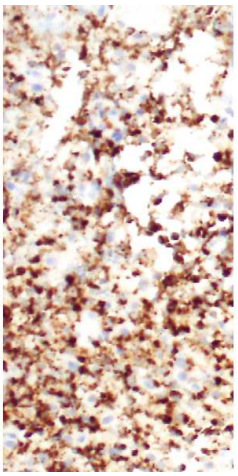
CD3



CD5



CD56



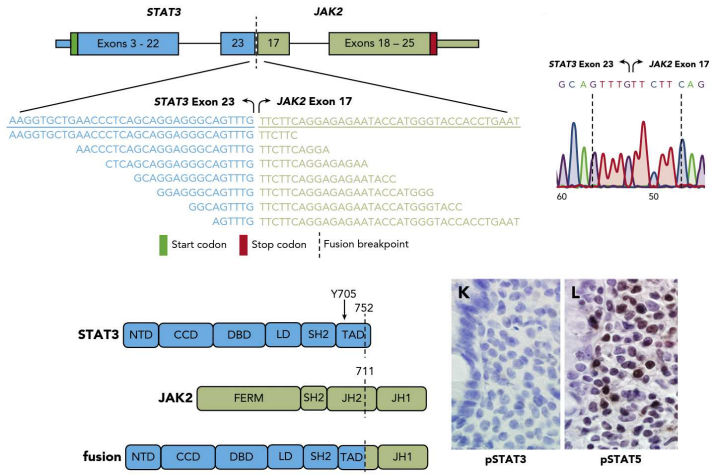
TIA

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

- can involve any part of the GI tract, most common in small bowel and colon; bone marrow and blood not involved
- CD2+, CD3+, CD7+/-, low Ki67, CD8+ > CD4+
- CD5+ alpha-beta+, negative for CD56 (unlike MEITL)
- EBER negative
- TCR clonal
- recurrent STAT3-JAK2 fusions (CD4+ > CD8+)

Recurrent *STAT3-JAK2* fusions in indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

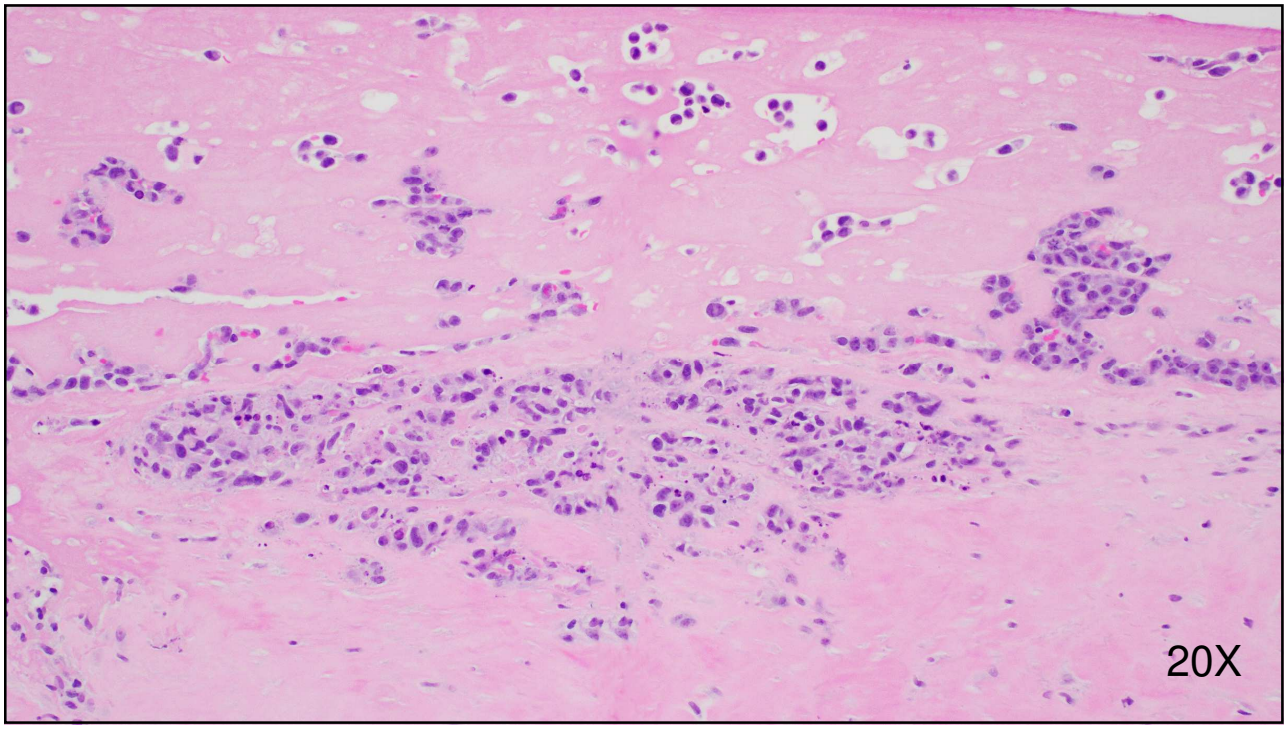
Ayush Sharma,[1] Naoki Oishi,[2,3] Rebecca L. Boddicker,[2] Guangzhen Hu,[2] Hailey K. Benson,[2] Rhett P. Ketterling,[2] Patricia T. Greipp,[2] Darlene L. Knutson,[2] Sara M. Kloft-Nelson,[2] Rong He,[2] Bruce W. Eckloff,[4] Jin Jen,[2] Asha A. Nair,[5] Jaime I. Davila,[5] Surendra Dasari,[5] Konstantinos N. Lazaridis,[1,6] N. Nora Bennani,[7] Tsung-Teh Wu,[2] Grzegorz S. Nowakowski,[6,7] Joseph A. Murray,[1,*] and Andrew L. Feldman[2,*]

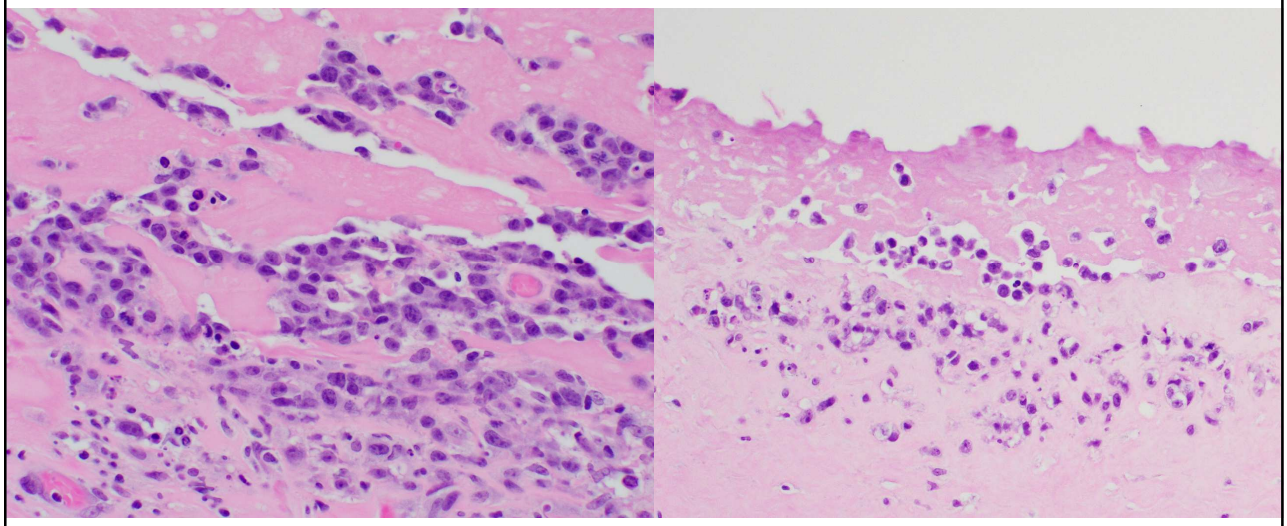


Anaplastic large cell lymphoma, breast implant-associated

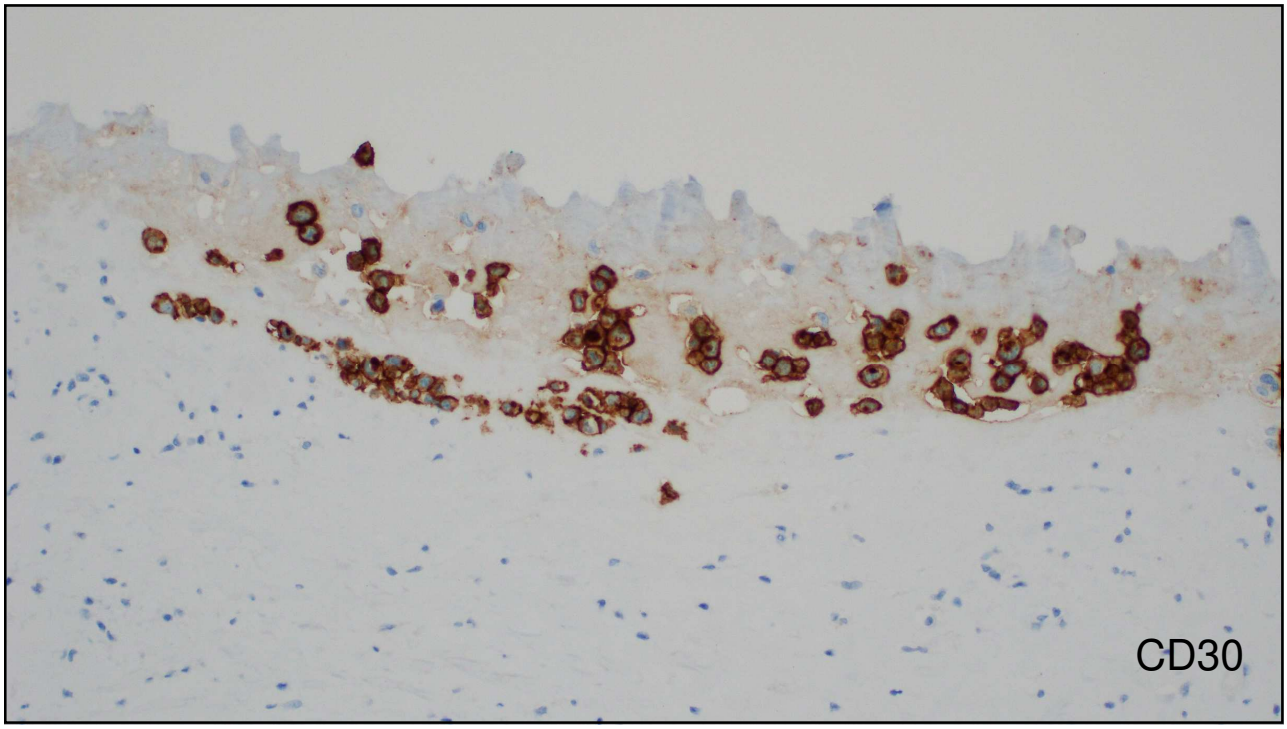
- CD30+
- T-cell phenotype (CD4+/-; granzyme B+)
- anaplastic lymphoma kinase-1-negative
- clonal T-cell receptor γ-chain gene rearrangements
- adjacent to silicone or saline breast implants; seroma associated

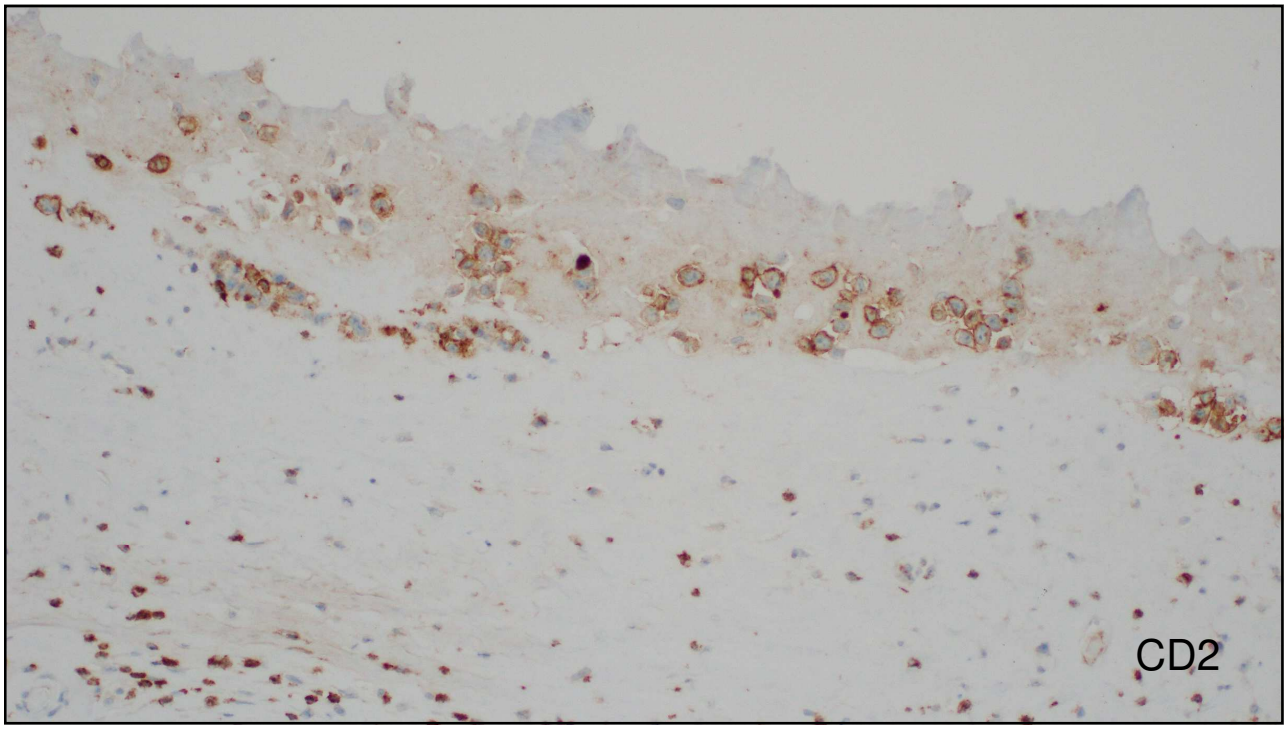
Case credit : Natasha Lewis, M.D.

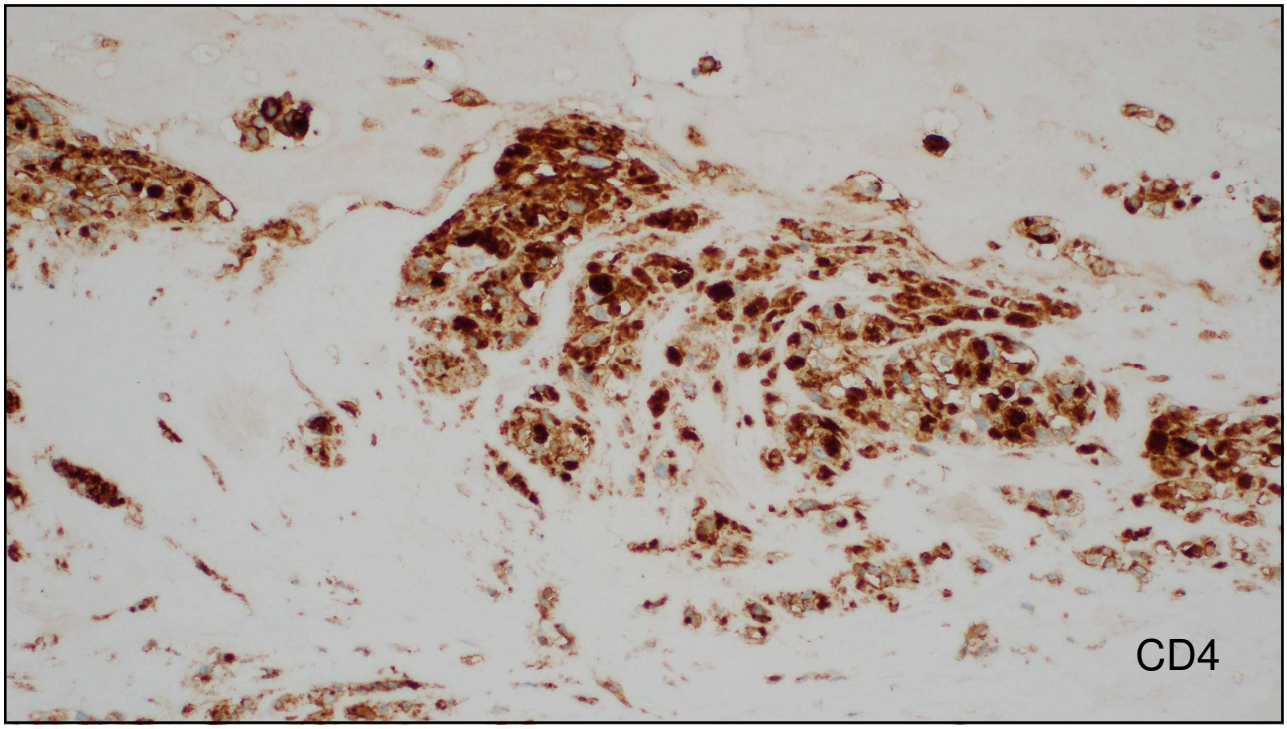




50X 20X




CD2


CD4

Outcomes for ALCL, breast implant-associated

Modern Pathology (2008) 21, 455–463 Roden, et al. series from Mayo and Michigan

Table 2 Clinical features of patients with anaplastic large-cell lymphoma in close proximity to breast implants

Patient	*Current study population*				*Review of the literature*				
	1	*2*	*3*	*4*	*5*[7]	*6*[5]	*7*[6]	*8*[6]	*9*[13]
Age (years)	45	59	34	44	33	41	87	50	72
Reason for implant	Breast cancer	Breast cancer	Cosmetic	Cosmetic	Cosmetic	Cosmetic	Breast cancer	Breast cancer	Breast cancer
Material of implant	Saline	Silicone	Saline	Saline	Silicone	Saline	Saline	Silicone	Silicone
Time implant to lymphoma (years)	7	3	4	NA	13[a]	5	8	9	16
Presentation	Seroma	Seroma	Seroma	Seroma	Seroma	Mass	Seroma, mass	Nodules	Skin ulcer
Surgical treatment	Implant removal capsulectomy (5 months after diagnosis)	Implant removal capsulectomy[b]	Implant removal capsulectomy	Implant removal capsulectomy	Implant removal capsulectomy	NA	NA	NA	Implant removal (6 months before diagnosis)
Radiation	No	Yes	Yes (after pregnancy)	NA	Yes	Yes	NA	No	No
Chemotherapy	No	No	Yes (after radiation)	NA	Yes	Yes	NA	Yes	No
Additional information	NA	NA	Pregnant (13 weeks)	No staging performed	NA	NA	NA	Hodgkin lymphoma (20 years prior)	No staging performed
F/U (months)	20	10	9	NA	12	NA	NA	12	NA
Outcome	Alive, disease-free	Alive, disease-free	Alive, disease-free	NA	Alive, disease-free	Complete remission	NA	Systemic ALCL after 12 months	NA

NA, information not available.

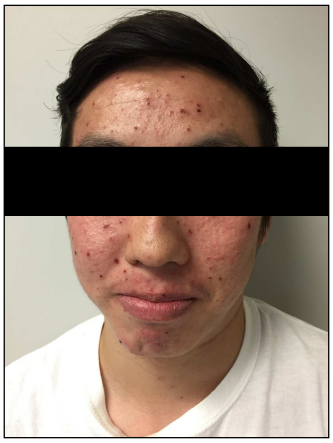
[a]Original implant was replaced after 9 years.

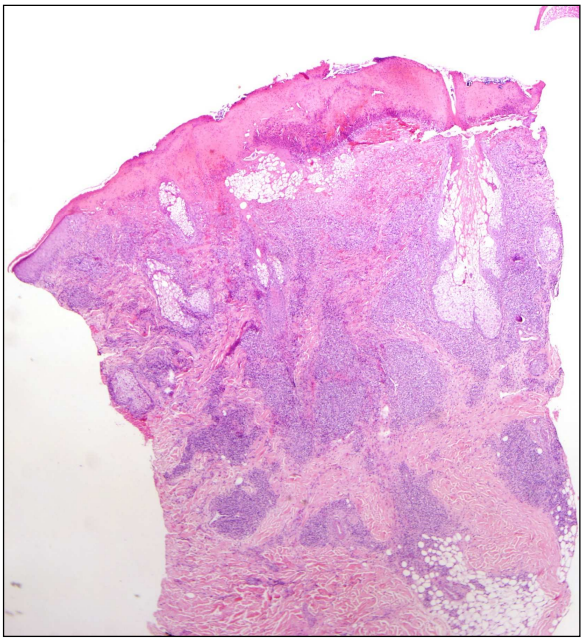
[b]Capsulectomy was performed at the time of implant removal.

Hydro vacciniforme (HV)-like LPD

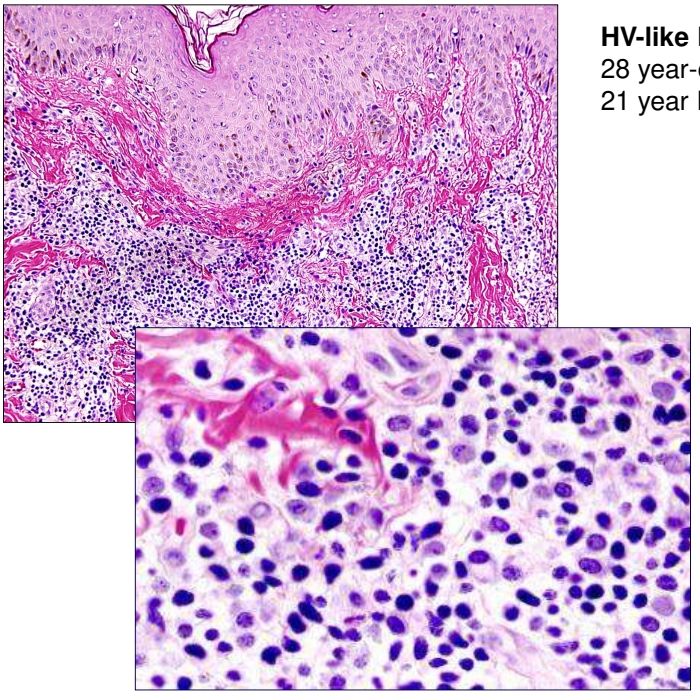
- Classified w. EBV+ T/NK cell LPDs of childhood
- poly-/ oligo-/ monoclonal LPD
- papulovesicular eruptions, ulceration, scarring
- infiltrates typically involve superficial dermis, w. epidermal reticular degeneration, intraepidermal spongiotic vesiculation
- Cytotoxic T or NK phenotype in skin; +/- γ-δ T cells in circulation

Case credits : Pallavi Kanwar Galera, M.D.

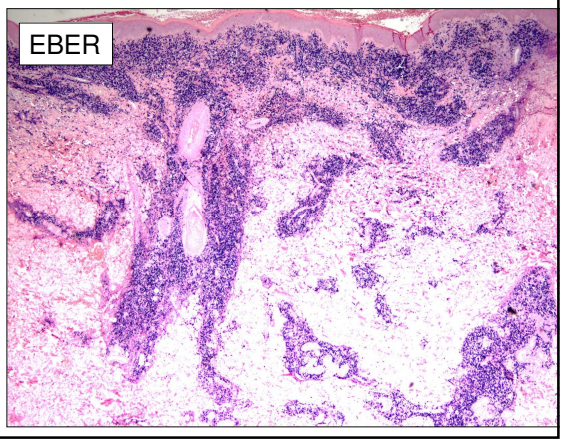




HV-like LPD
21 year-old Asian male
8-9 year history of skin eruptions, mouth sores



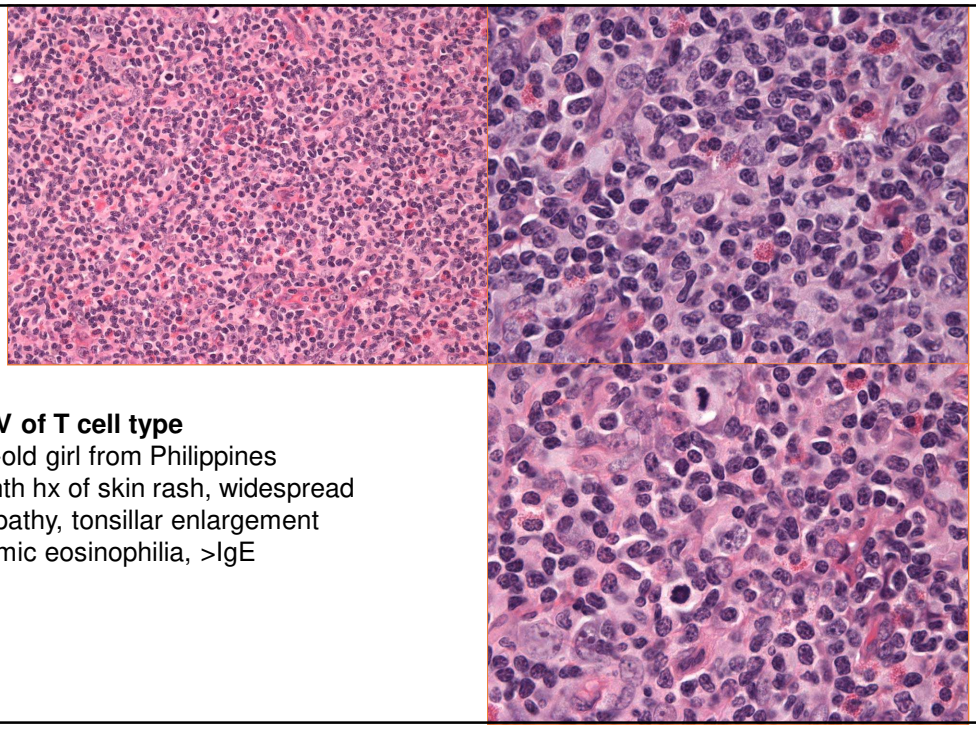
HV-like LPD
28 year-old Peruvian male
21 year history of skin lesions



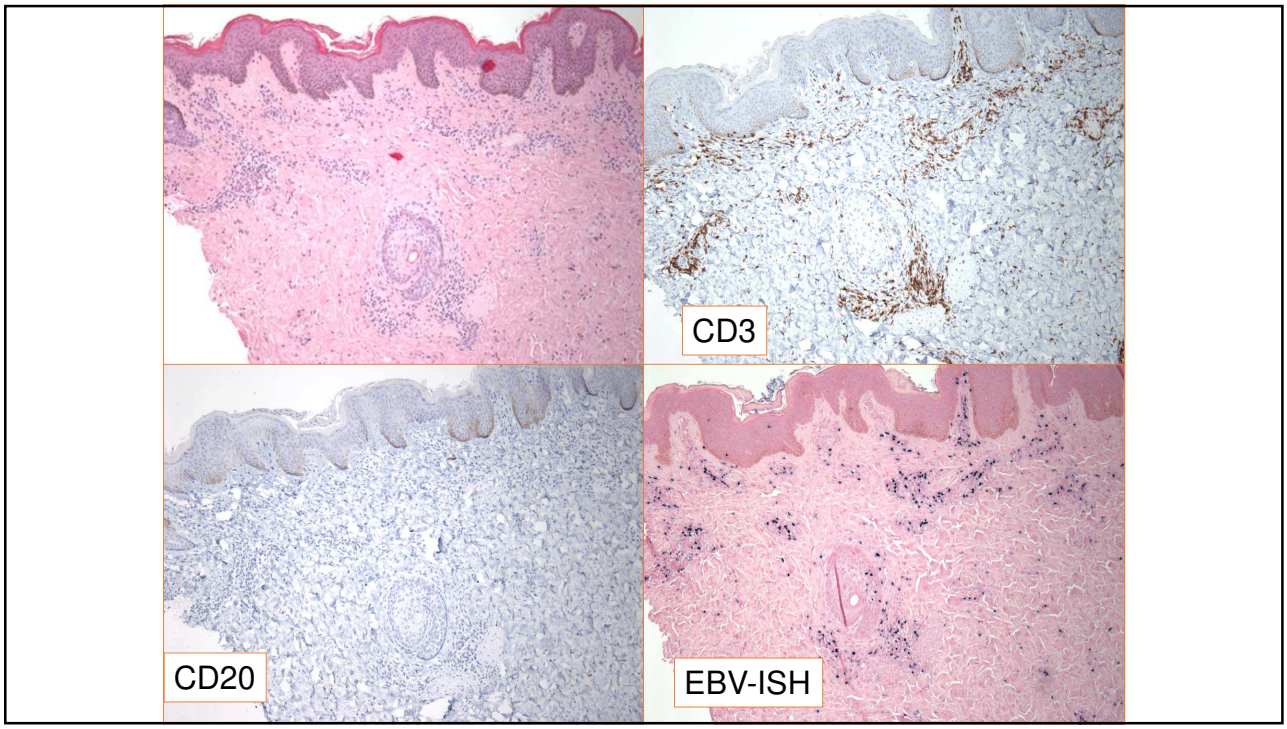
Chronic active EBV infection of T/NK type

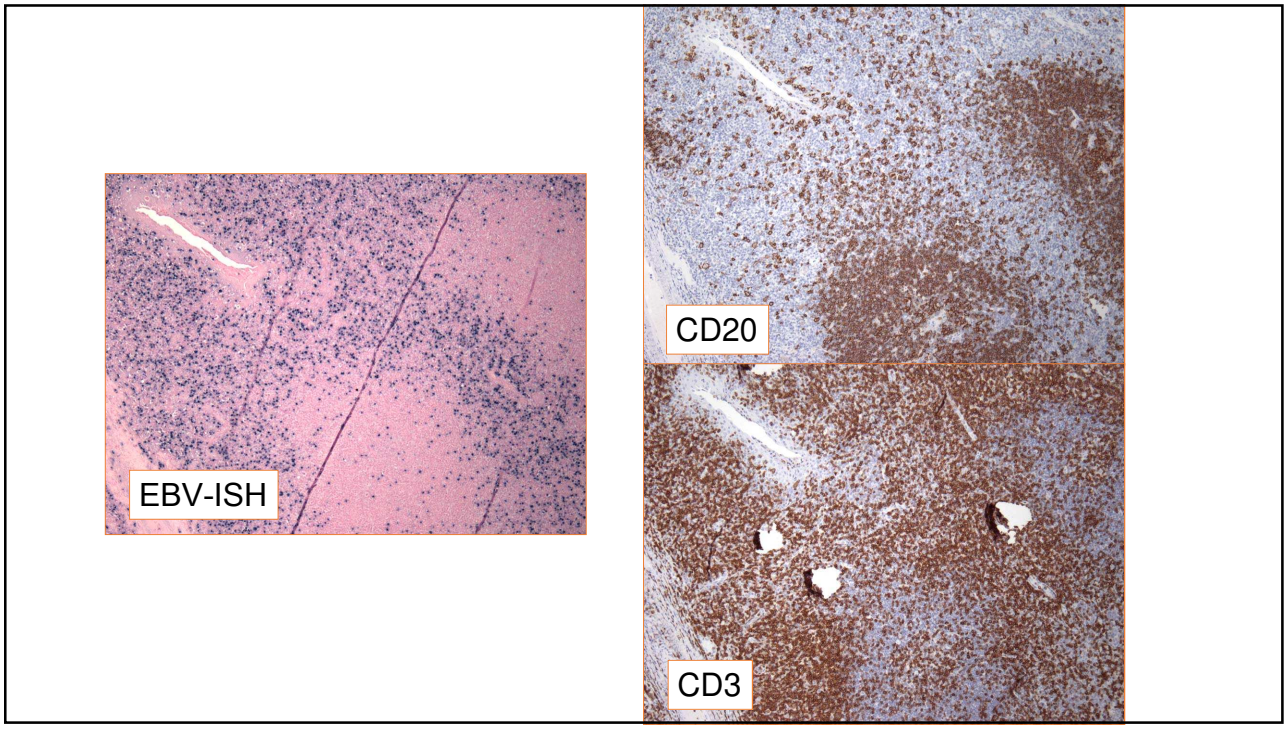
- poly-/ oligo-/ monoclonal LPD
- >3 mo. Increased EBV >$10^{2.5}$ copies/mg in blood
- EBER in tissue in T-cells (59%) or NK-cells (41%)
- present with infectious mono-like illness, +/- rash
- variable clinical course; some cases are indolent, some progress quickly to liver dysfunction, hemophagocytic syndrome

Case credit : Pallavi Kanwar Galera, M.D.



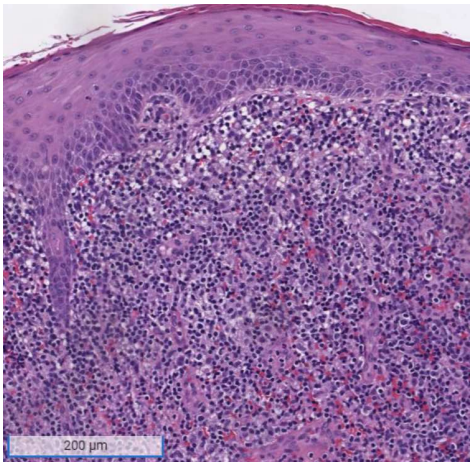
CAEBV of T cell type
8 year-old girl from Philippines
•1 month hx of skin rash, widespread adenopathy, tonsillar enlargement
•Systemic eosinophilia, >IgE

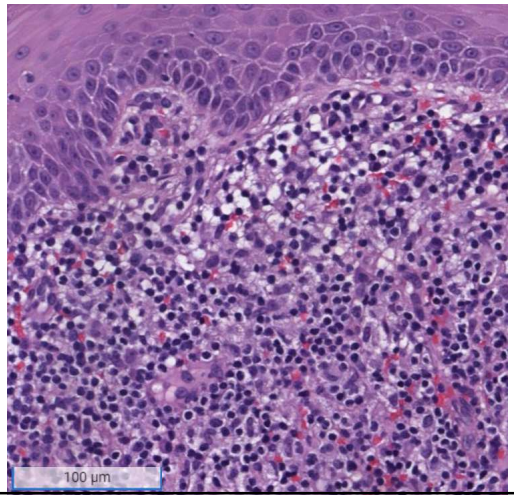

CD3
CD20
EBV-ISH

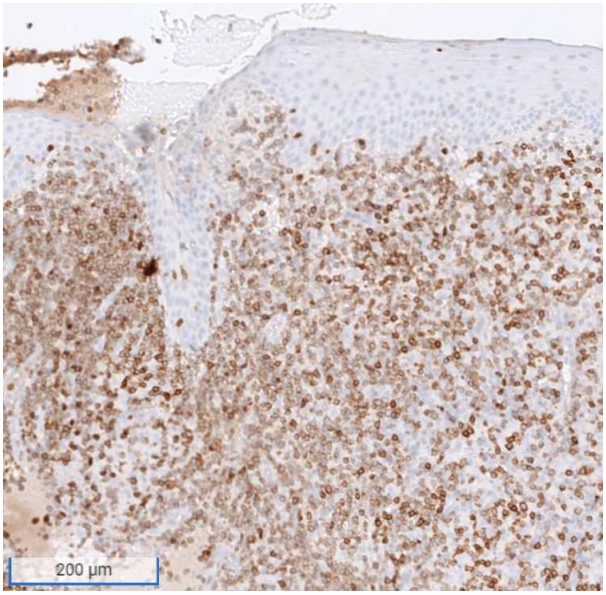

EBV-ISH
CD20
CD3

“indolent” NK/T cell lymphoma of the sinus (small cell variant)

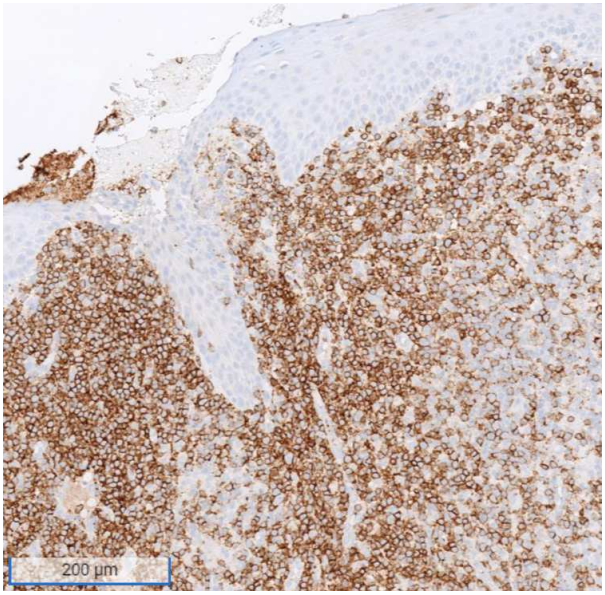
Case credit : Laura Wake, M.D.



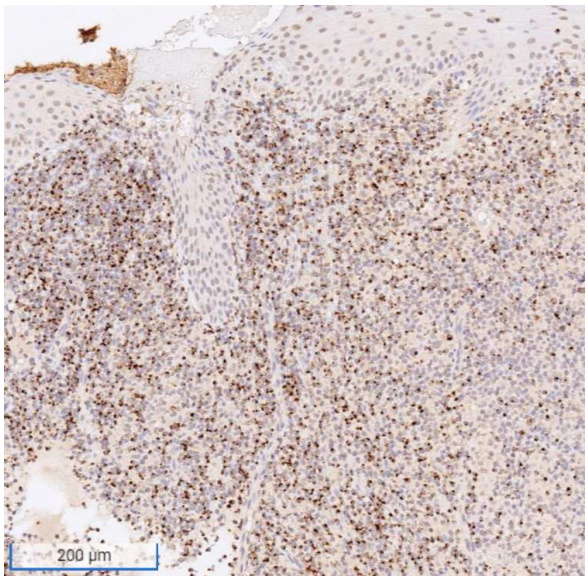




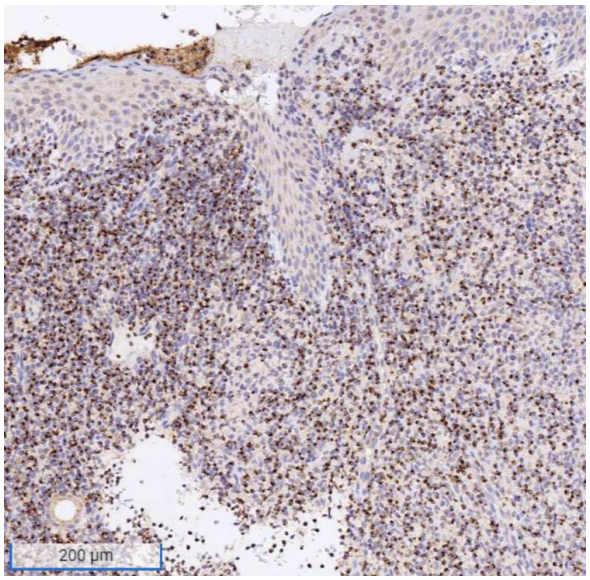
CD3



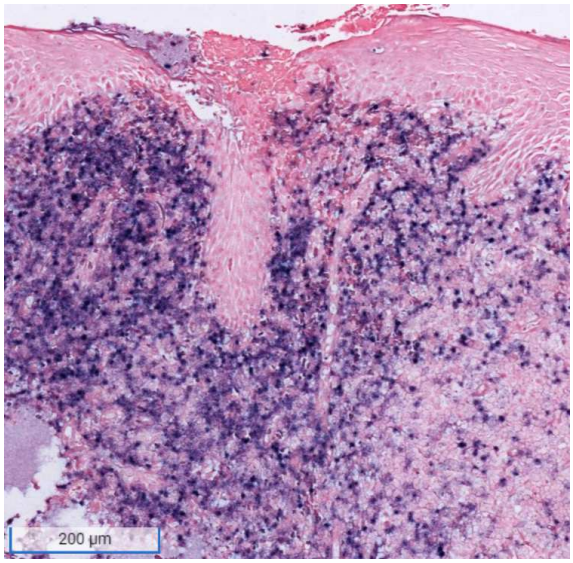
CD56



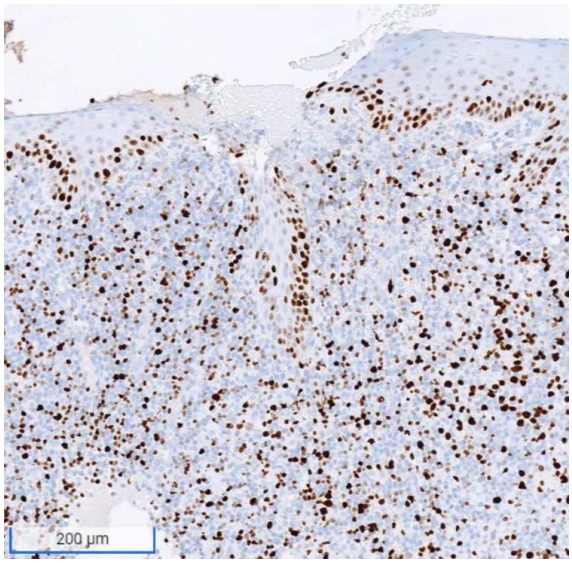
granzyme



TIA



EBER



Ki67

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Cases from :

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