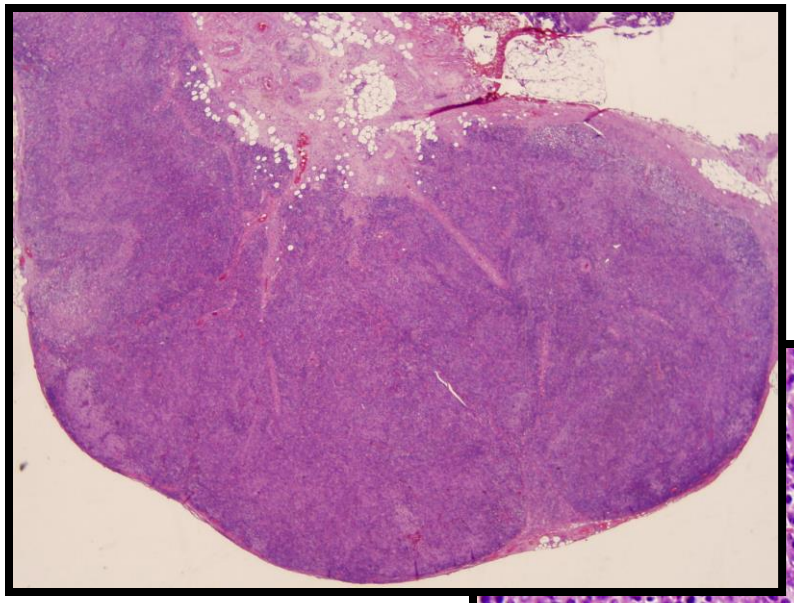
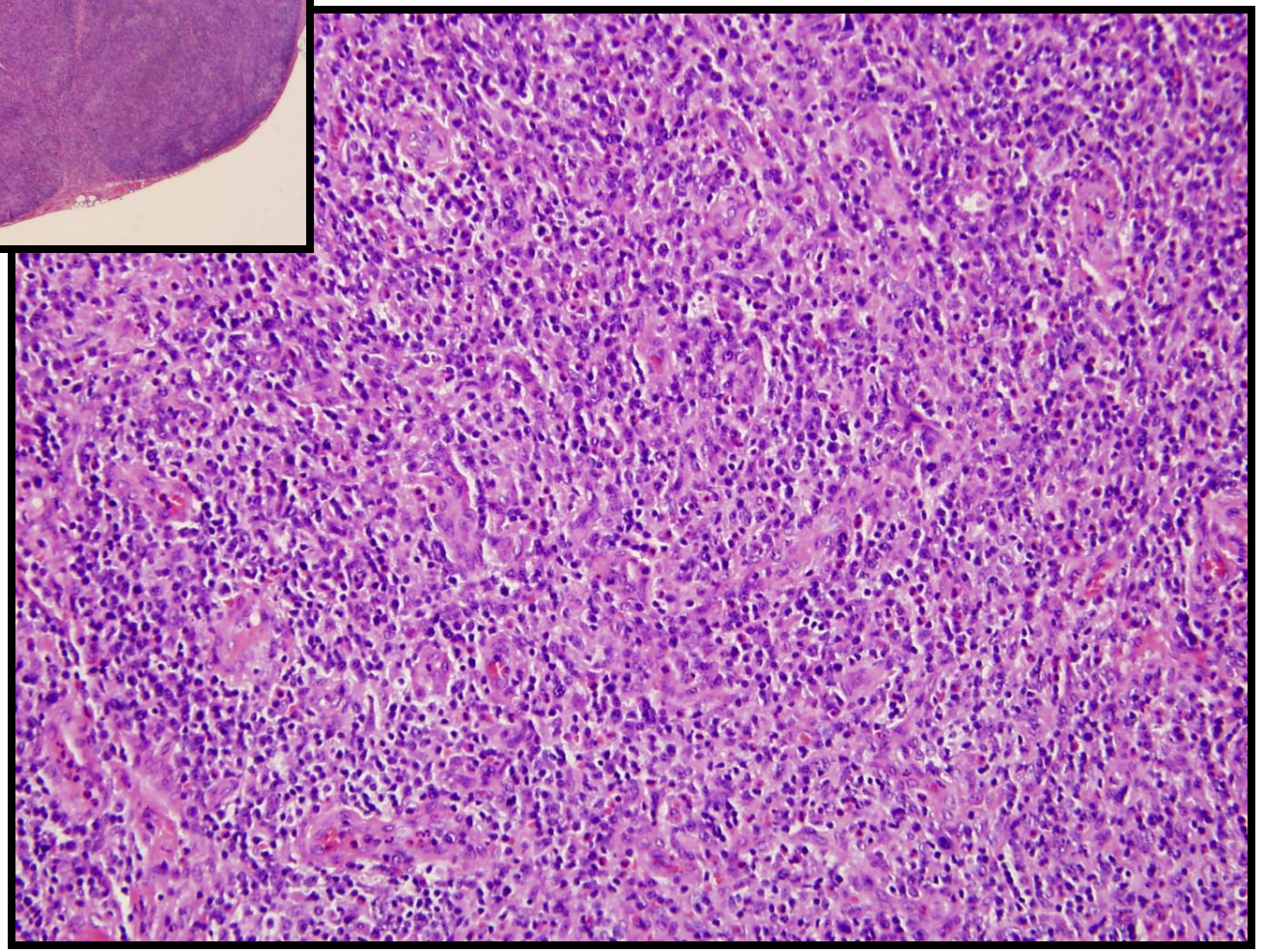
CASE 7

A 51-year-old woman with a history of breast cancer developed cervical lymphadenopathy. Needle biopsy showed atypical follicular hyperplasia. She was followed. One year later she developed dyspnea, fatigue and widespread lymphadenopathy. A right inguinal lymph node was excised.

Case 7





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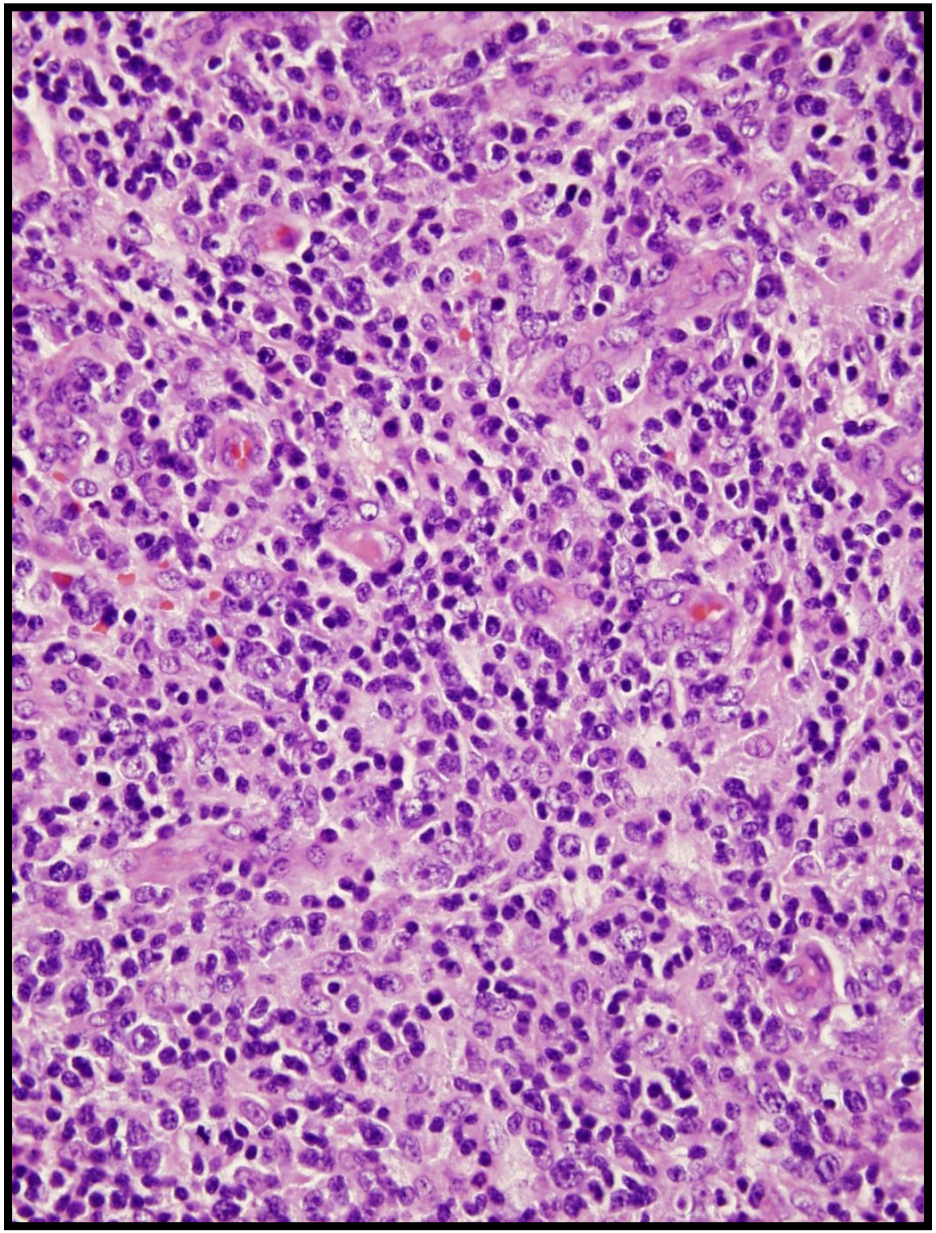

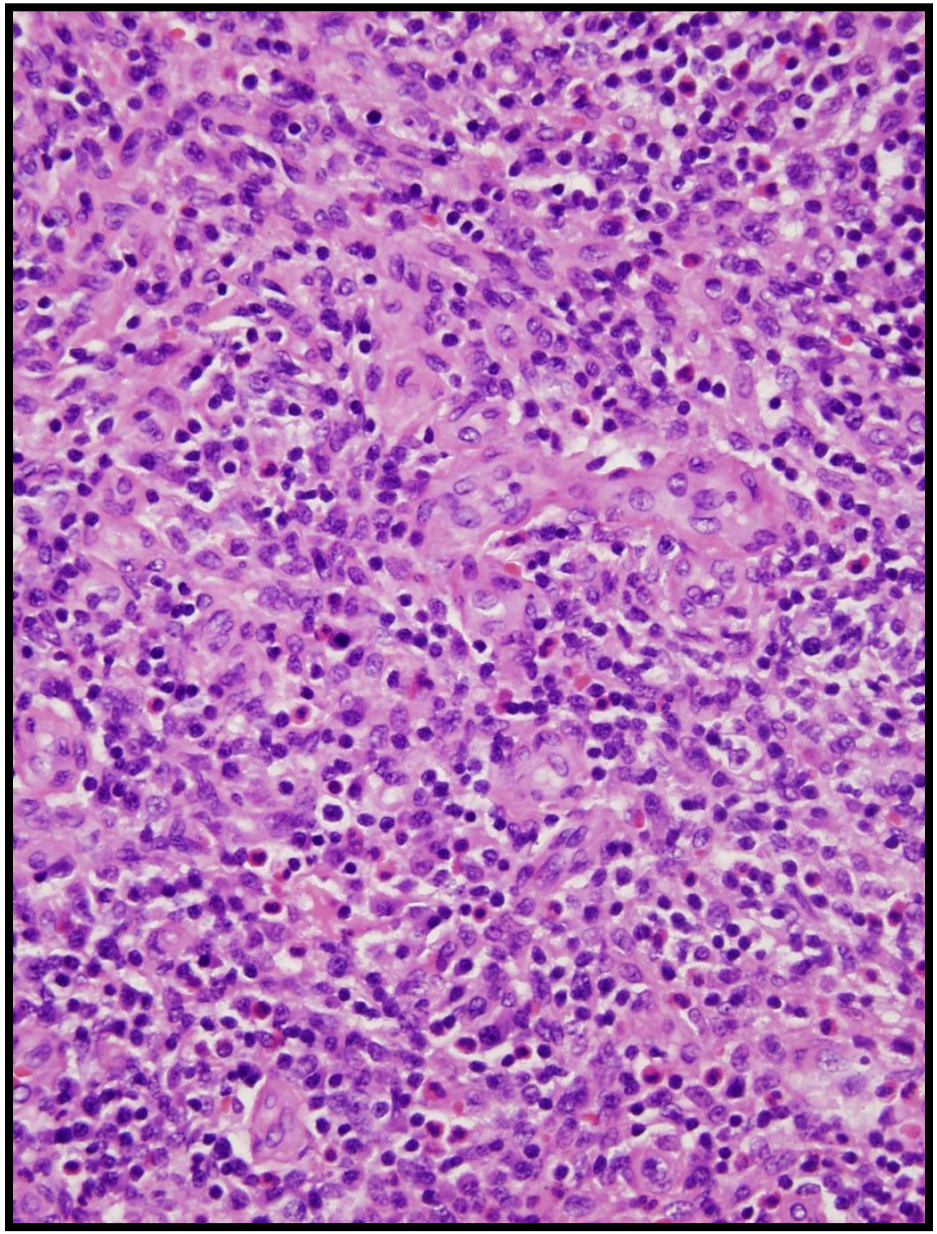

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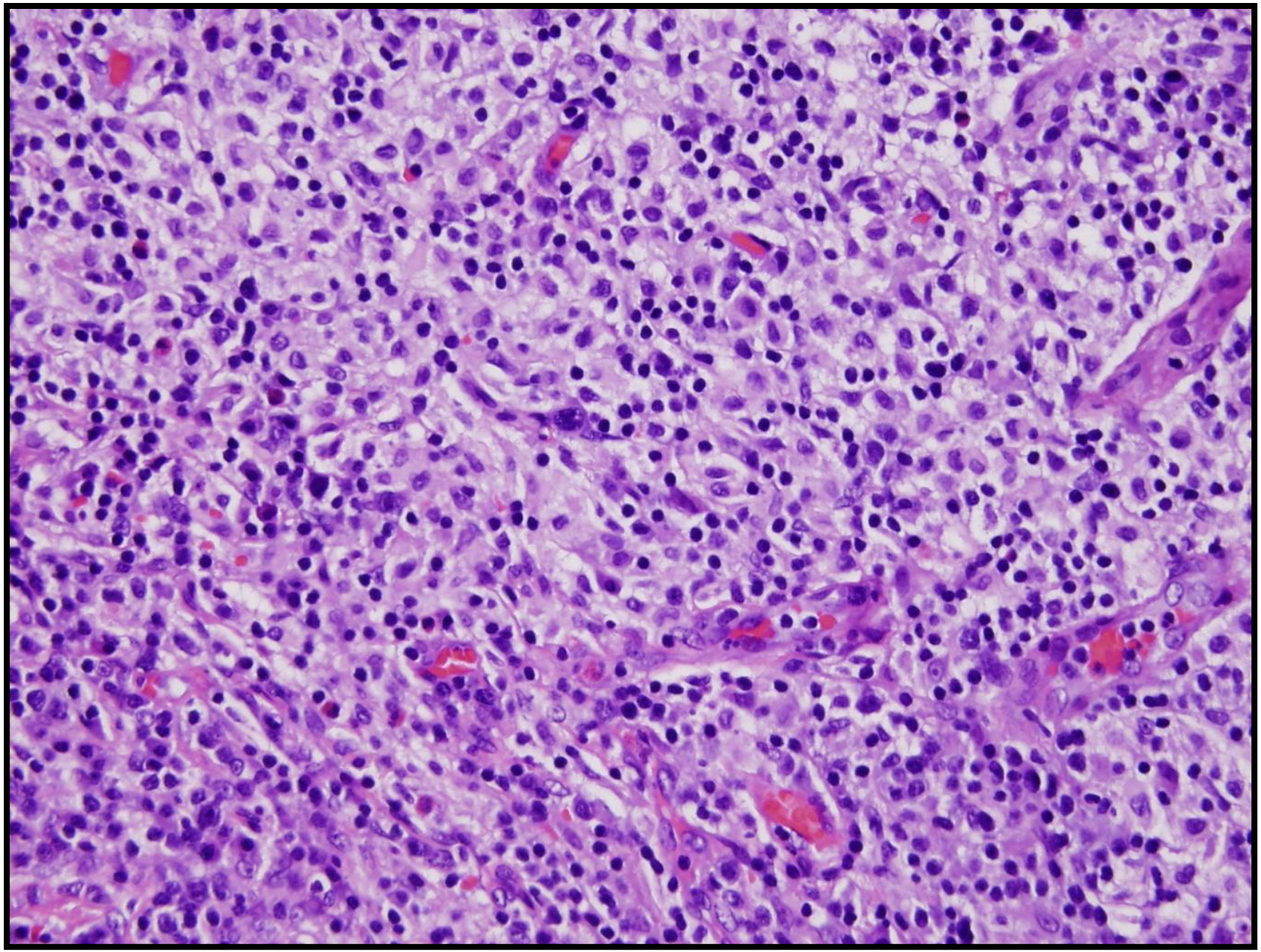

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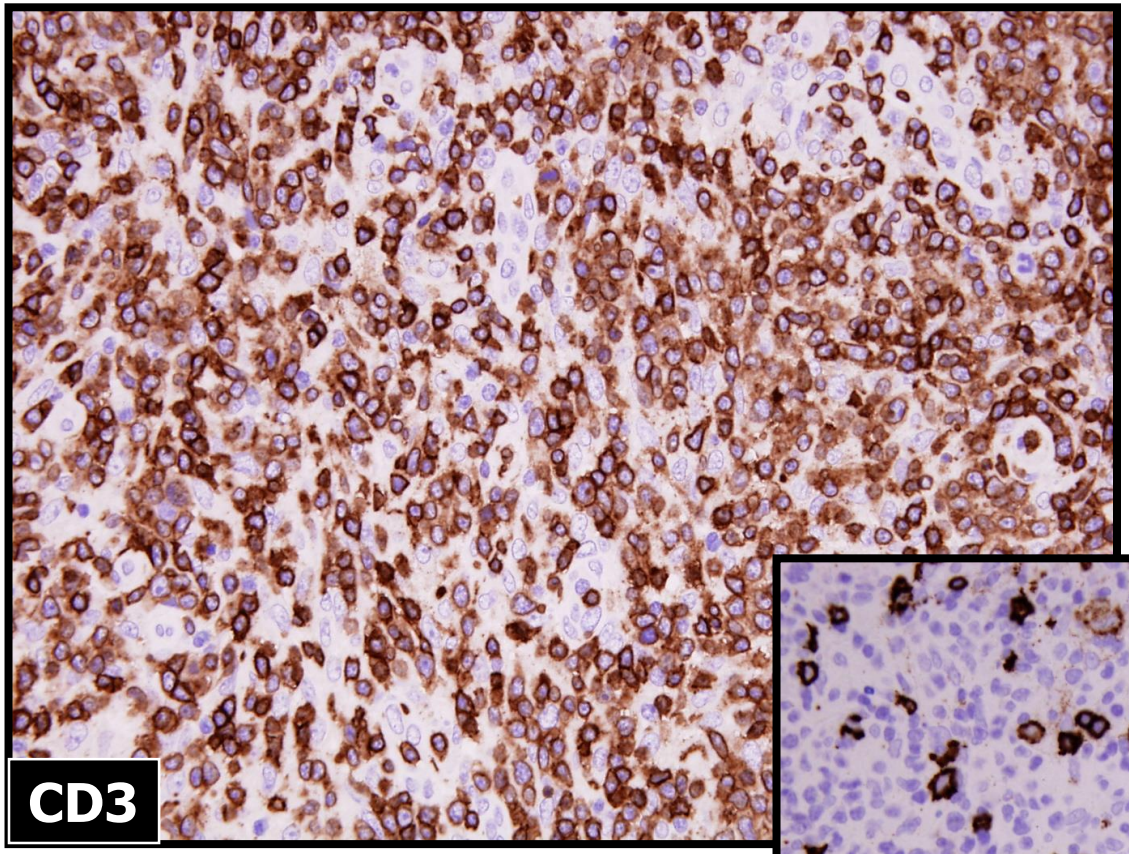

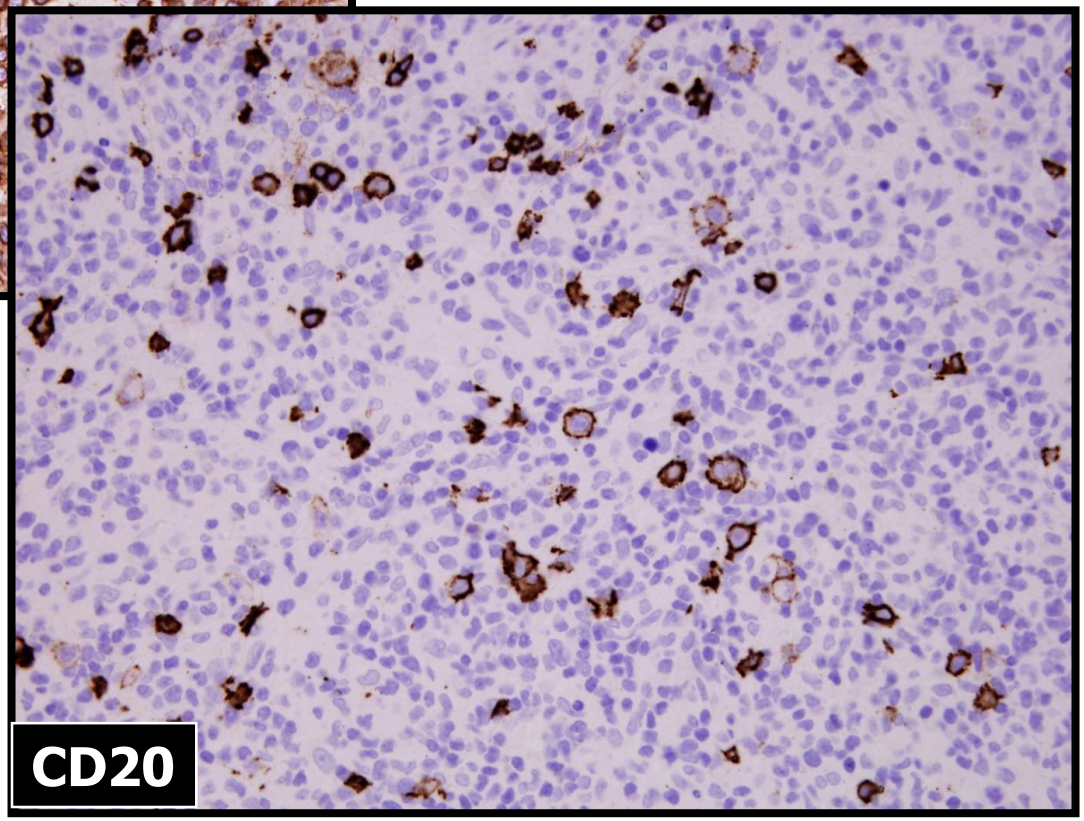

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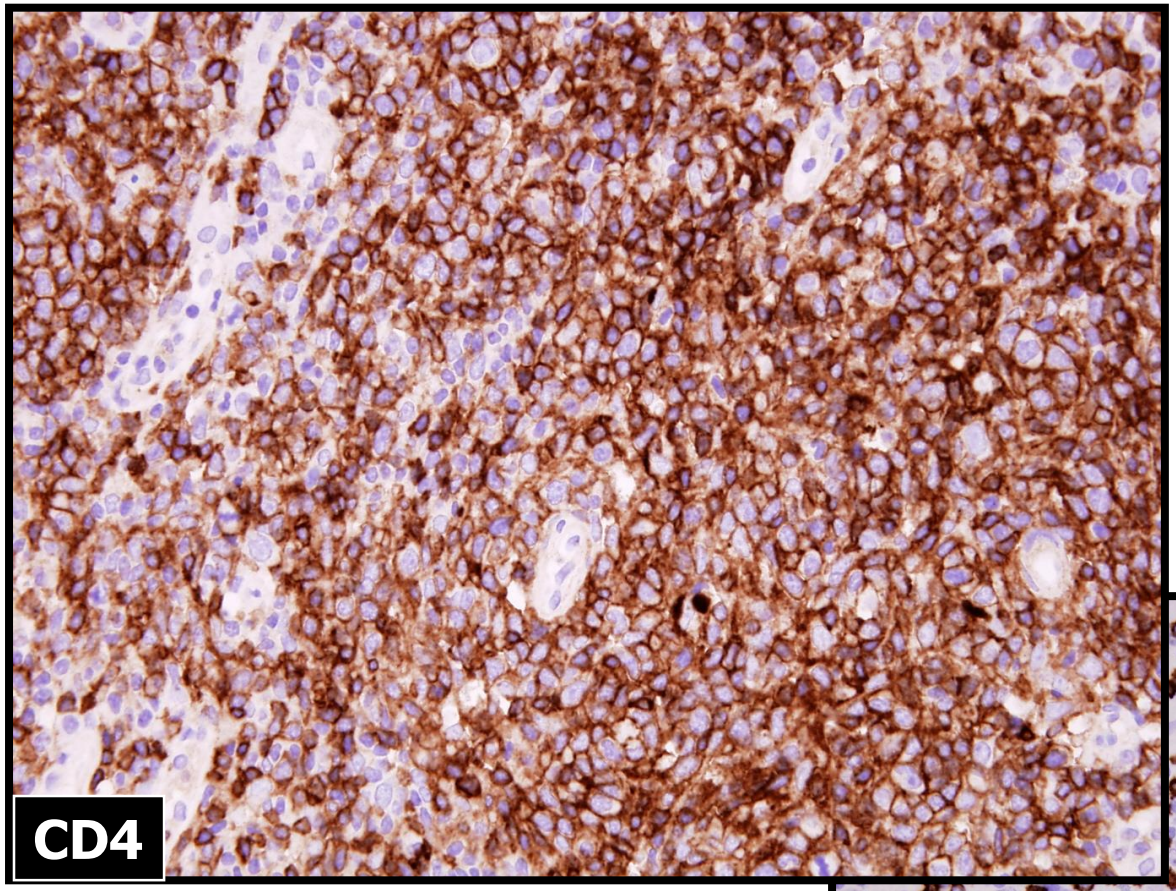

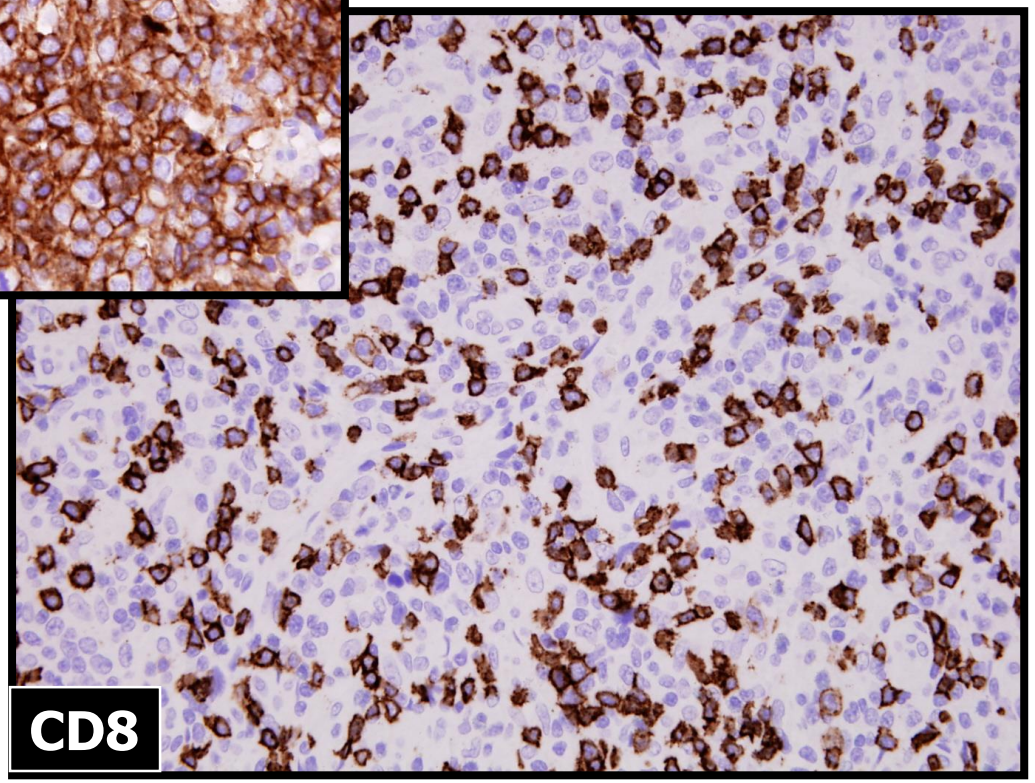

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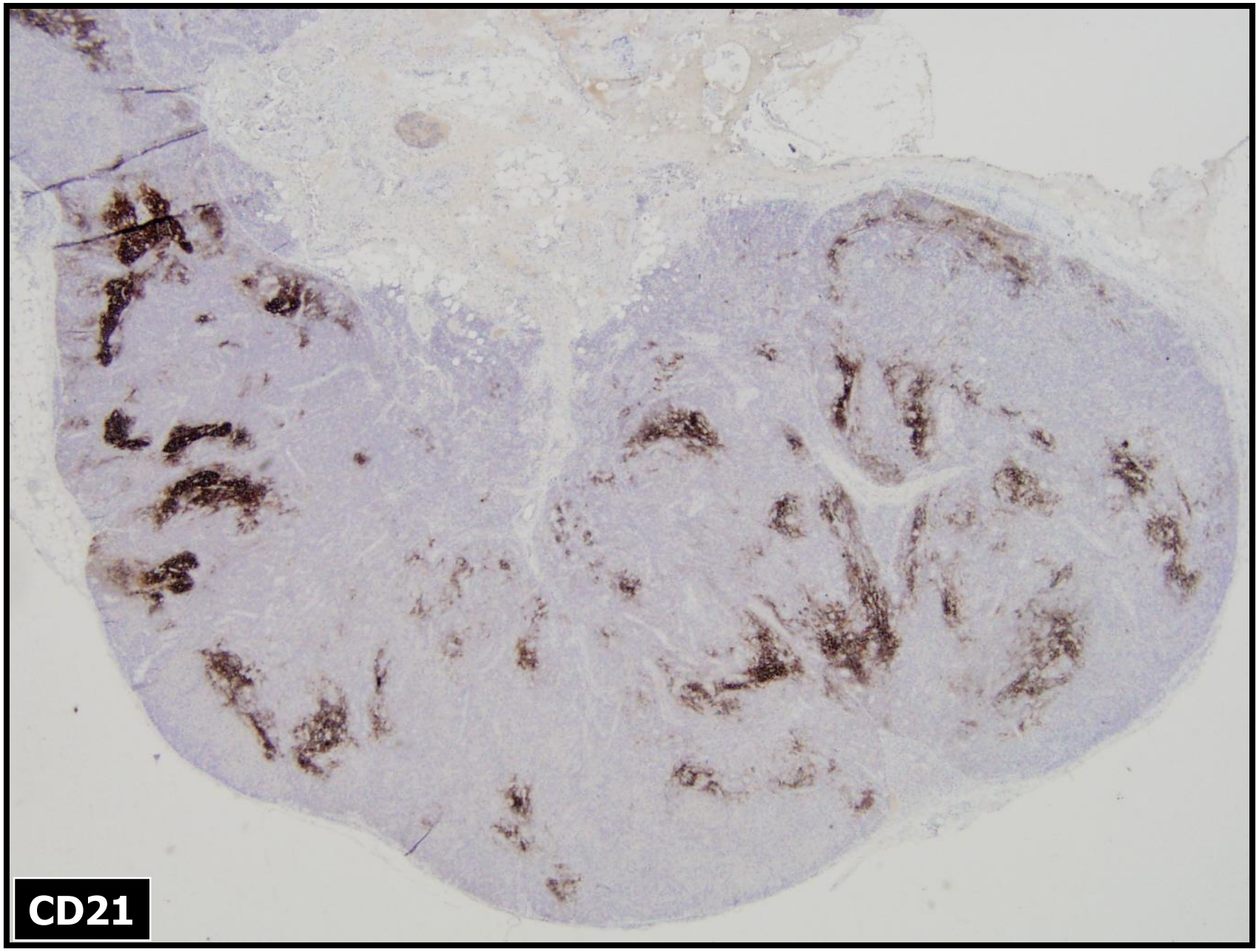

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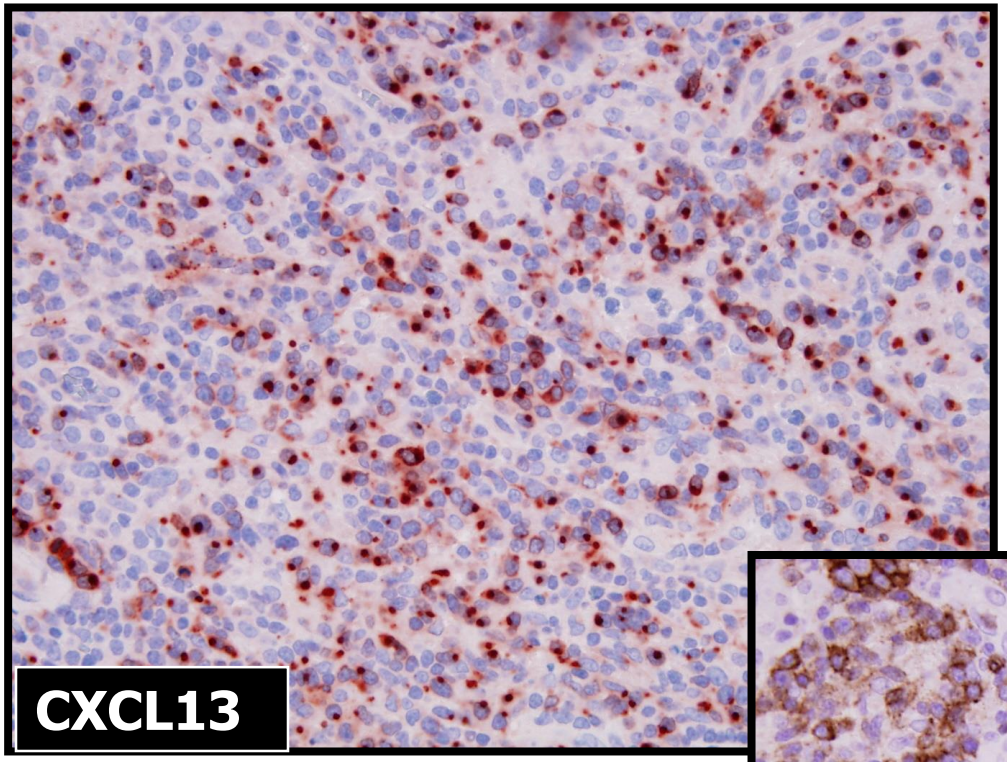
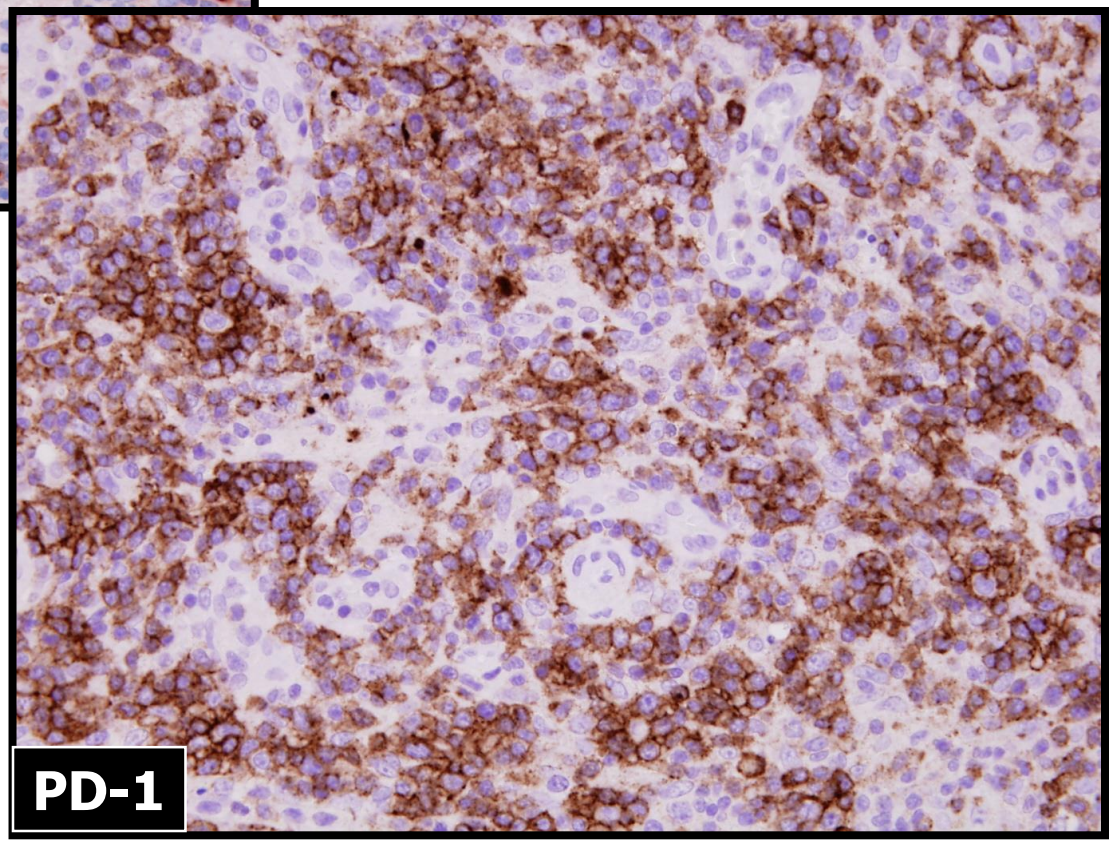
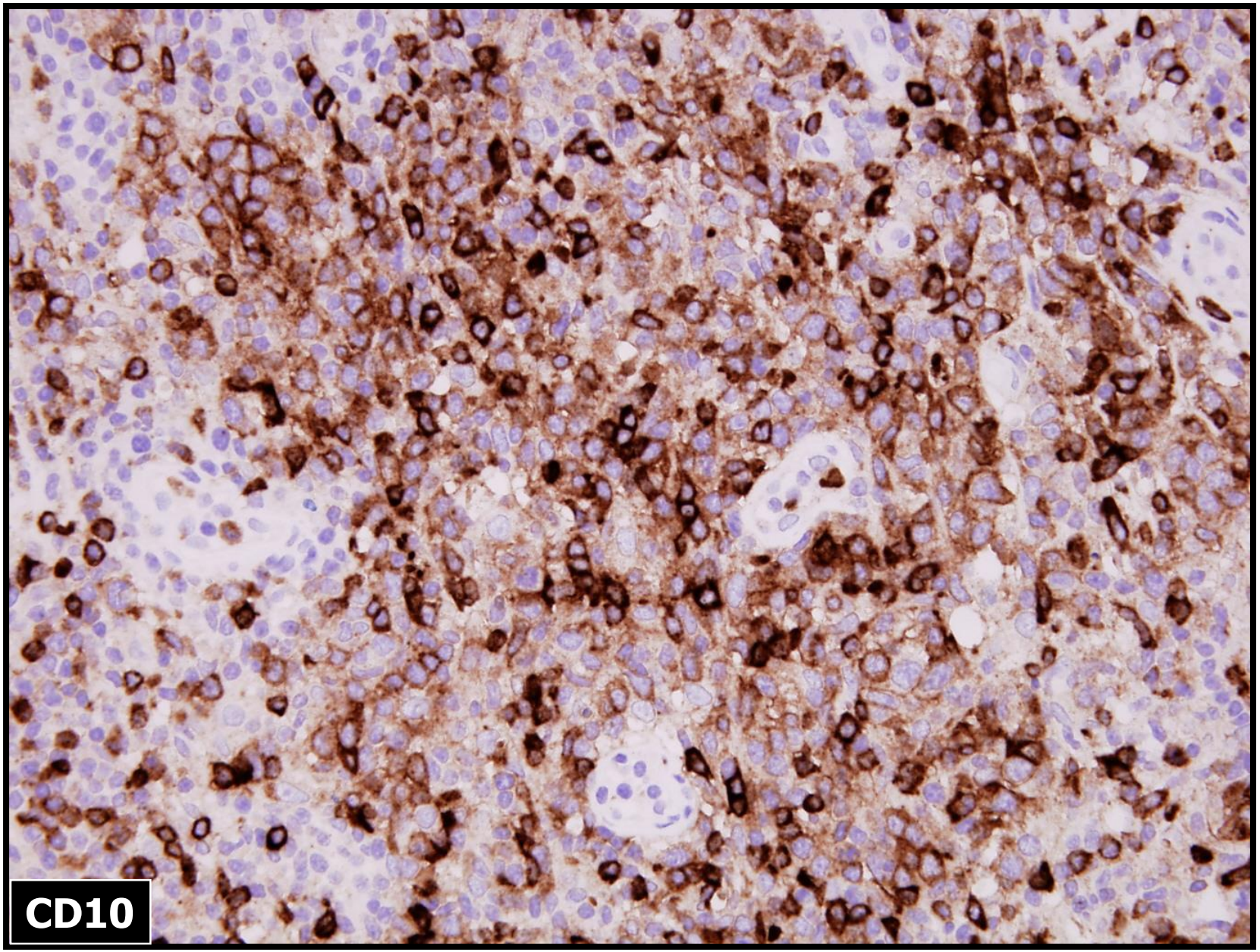





CD10

DIAGNOSIS (CASE 7)

Angioimmunoblastic T-cell lymphoma

Lymphoma Categories in WHO Classification
2017 Revision

Precursor lymphoid neoplasms	9/1
Mature B-cell neoplasms	50
Mature T-cell and NK-cell neoplasms	28
Hodgkin Lymphoma	5
Histiocytic and dendritic cell neoplasms	9
Immunodeficiency-associated lymphoproliferative disorders	8
	93

T/NK-cell Lymphomas – WHO 2017

5 General Disease Categories

Leukemic or Disseminated

Extranodal

Cutaneous

Nodal

Immature / Lymphoblastic

T/NK-cell Lymphomas – WHO 2017

Leukemic or Disseminated

T-cell prolymphocytic leukemia

T-cell large granular lymphocytic leukemia

Chronic lymphoproliferative disorders of NK cells

Aggressive NK-cell leukemia

Adult T-cell leukemia/lymphoma

Systemic EBV+ T-cell lymphoma of childhood

T/NK-cell Lymphomas – WHO 2017
Extranodal

Extranodal NK/T-cell lymphoma, nasal type

Enteropathy-associated T-cell lymphoma (ETL)

Monomorphic epitheliotropic intestinal T-cell lymphoma (previously type II ETL)

Hepatosplenic T-cell lymphoma

Indolent T-cell LPD of GI tract

Breast implant associated ALCL

T/NK-cell Lymphomas – WHO 2017

Cutaneous

Mycosis fungoides

Sezary syndrome

Primary cutaneous CD30+ T-cell LPD

- **Lymphomatoid papulosis**
- **Primary cutaneous ALCL**

Subcutaneous panniculitis-like T-cell lymphoma

Primary cutaneous gamma-delta T-cell lymphoma

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma

Primary cutaneous acral CD8+ lymphoma

Primary cutaneous CD4+ small/medium T-cell LPD

Hydroa vacciniforme-like LPD

T/NK-cell Lymphomas – WHO 2017

Nodal

Mature immunophenotype

Peripheral T-cell lymphoma NOS

Nodal PTCL with TFH phenotype

Follicular T-cell lymphoma, NOS

Anaplastic large cell lymphoma, ALK+

Anaplastic large cell lymphoma, ALK-

Angioimmunoblastic T-cell lymphoma

Immature (usually TdT+)

T-lymphoblastic lymphoma / leukemia

Angioimmunoblastic T-cell Lymphoma
History

First described as lymphogranulomatosis X in 1954 (in German)

Re-described in 1974 by 2 groups as:

- **Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD)**
- **Immunoblastic lymphadenopathy**

The name AILD became popular

Initially thought to be a pre-neoplastic

First Paper Using AILD Designation

ANGIO-IMMUNOBLASTIC LYMPHADENOPATHY WITH DYSPROTEINAEMIA

G. FRIZZERA E. M. MORAN
H. RAPPAPORT

Department of Pathology and Medicine, University Chicago Pritzker School of Medicine, and Franklin McLean Memorial Research Institute, Chicago, Illinois 60637, U.S.A.

THE LANCET, JUNE 1, 1974

Angioimmunoblastic T-cell Lymphoma

History

1970s Patients with AILD have poor prognosis

1980s First descriptions of AILD-like lymphoma
Molecular studies often showed clonality in both AILD and AILD-like lymphoma

1994 REAL classification renames AILD as angioimmunoblastic T-cell lymphoma (AITL)

2001 AITL adopted by WHO classification

2007 Recognition that AITL is of T-follicular helper cell lineage

2017 PTCL with TFH immunophenotype adopted by WHO classification (in addition to AITL)

The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (T_{FH}) cells

Laurence de Leval,[1] David S. Rickman,[2] Caroline Thielen,[1] Aurélien de Reynies,[2] Yen-Lin Huang,[3,5] Georges Delsol,[6] Laurence Lamant,[6] Karen Leroy,[3,4,5] Josette Brière,[7] Thierry Molina,[8] Françoise Berger,[9] Christian Gisselbrecht,[10] Luc Xerri,[11] and Philippe Gaulard[3,4,5]

Laurence de Leval, MD

Philippe Gaulard, MD

Angioimmunoblastic T-cell Lymphoma

Definition

"AITL is a neoplasm of mature T follicular helper (TFH) cells characterized by systemic disease and a polymorphous infiltrate involving lymph nodes, with a prominent proliferation of high endothelial venules and follicular dendritic cells. EBV-positive B-cells are nearly always present, and in some cases constitute a significant part of the cellular infiltrate. Recent studies using next generation sequencing have identified recurrent mutations that help to unify AITL with other T-cell neoplasms derived from TFH cells. The disease is clinically aggressive and seen mainly in older patients."

2017 WHO book, p 408

Angioimmunoblastic T-cell Lymphoma

Symptoms and Physical Findings

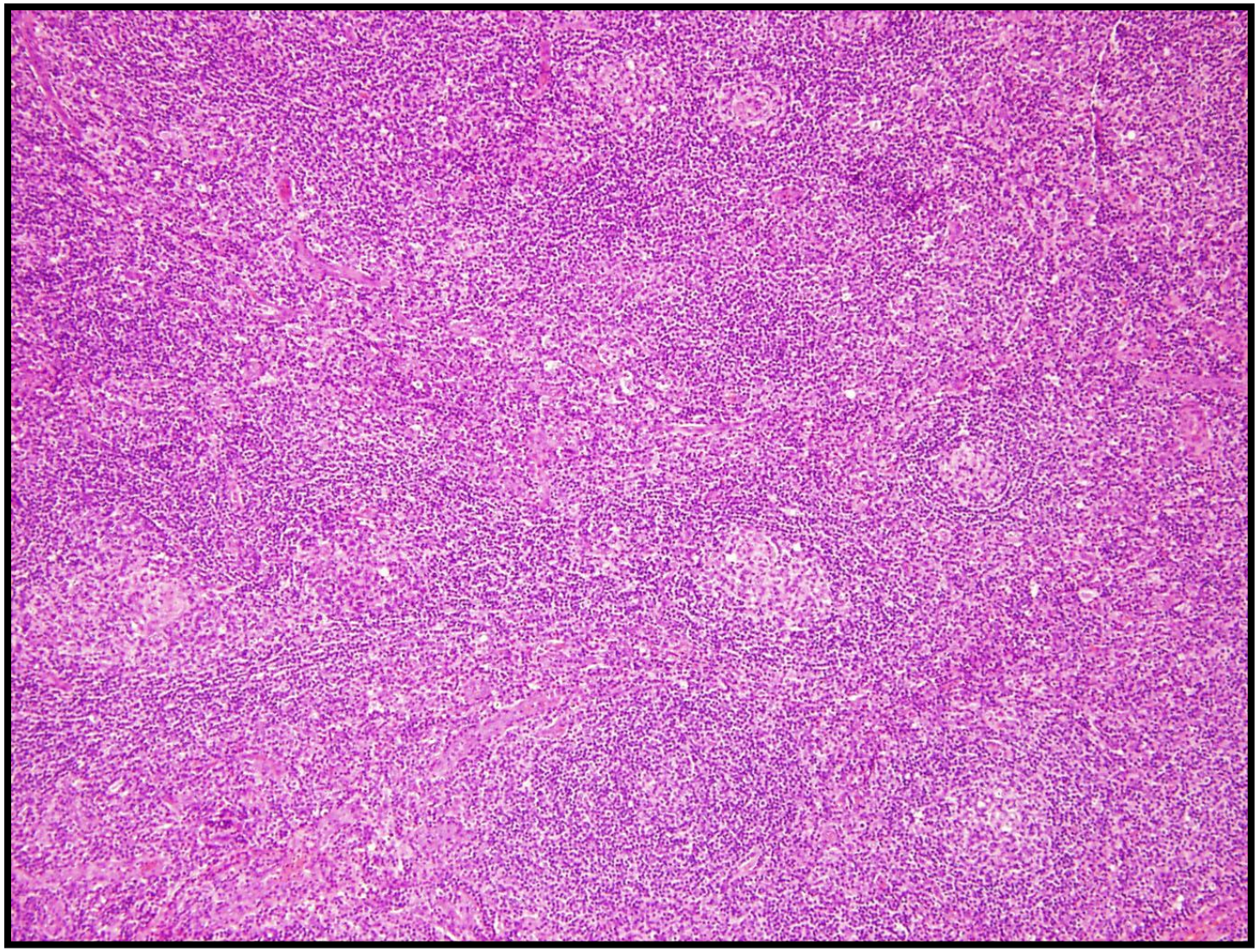
Generalized lymphadenopathy	**94-97 %**
B symptoms	**68-85 %**
Splenomegaly	**70-73 %**
Hepatomegaly	**52-72 %**
Skin rash	**48-58 %**
Ascites/effusions	**23-37 %**

Angioimmunoblastic T-cell Lymphoma
Laboratory Findings

Hypergammaglobulinemia	**50-83 %**
Autoantibodies	**66-77 %**
Elevated LDH	**70-74 %**
Anemia	**40-57 %**
Elevated ESR	**40-45 %**
Eosinophilia	**30-40 %**

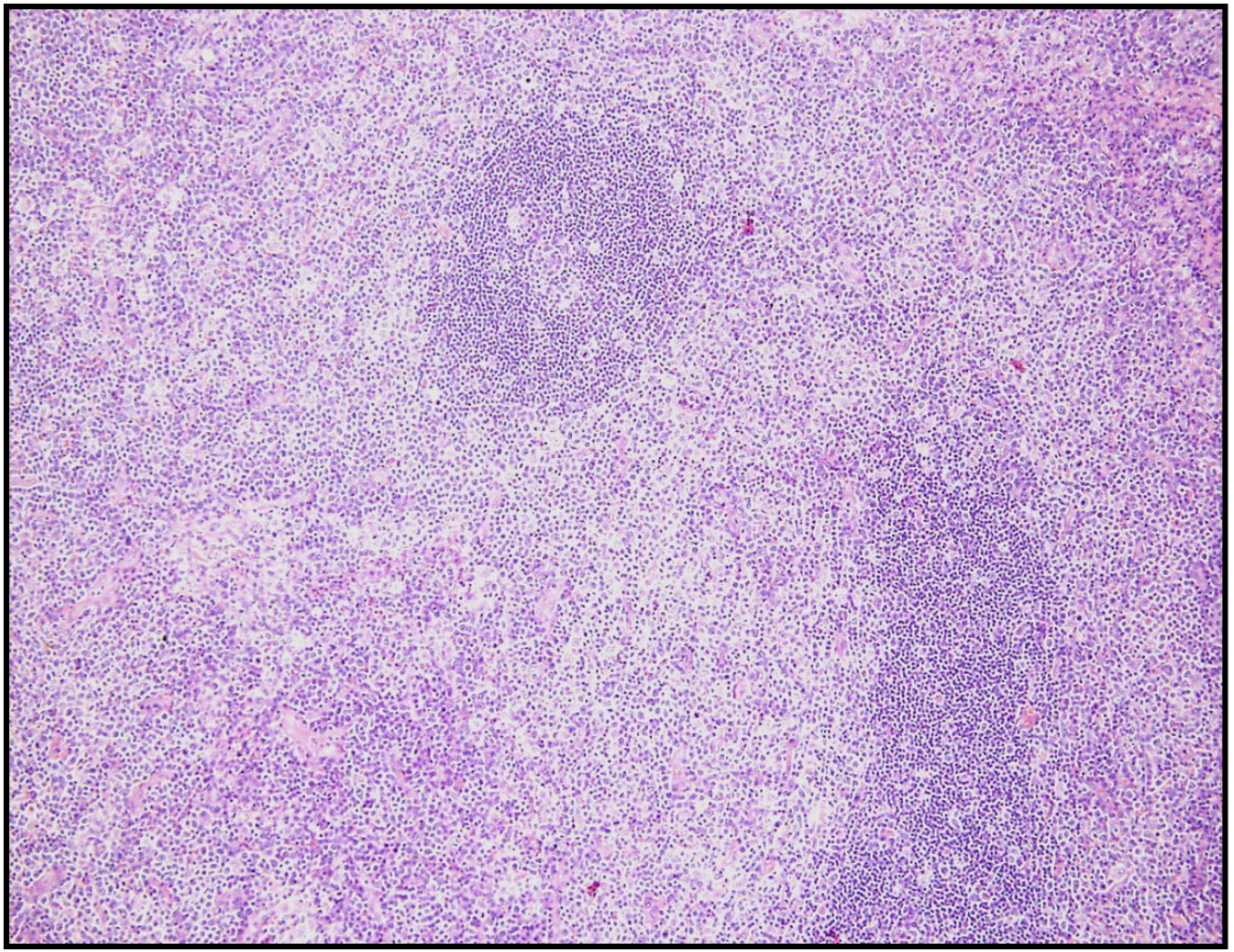
Angioimmunoblastic T-cell Lymphoma

Pattern I



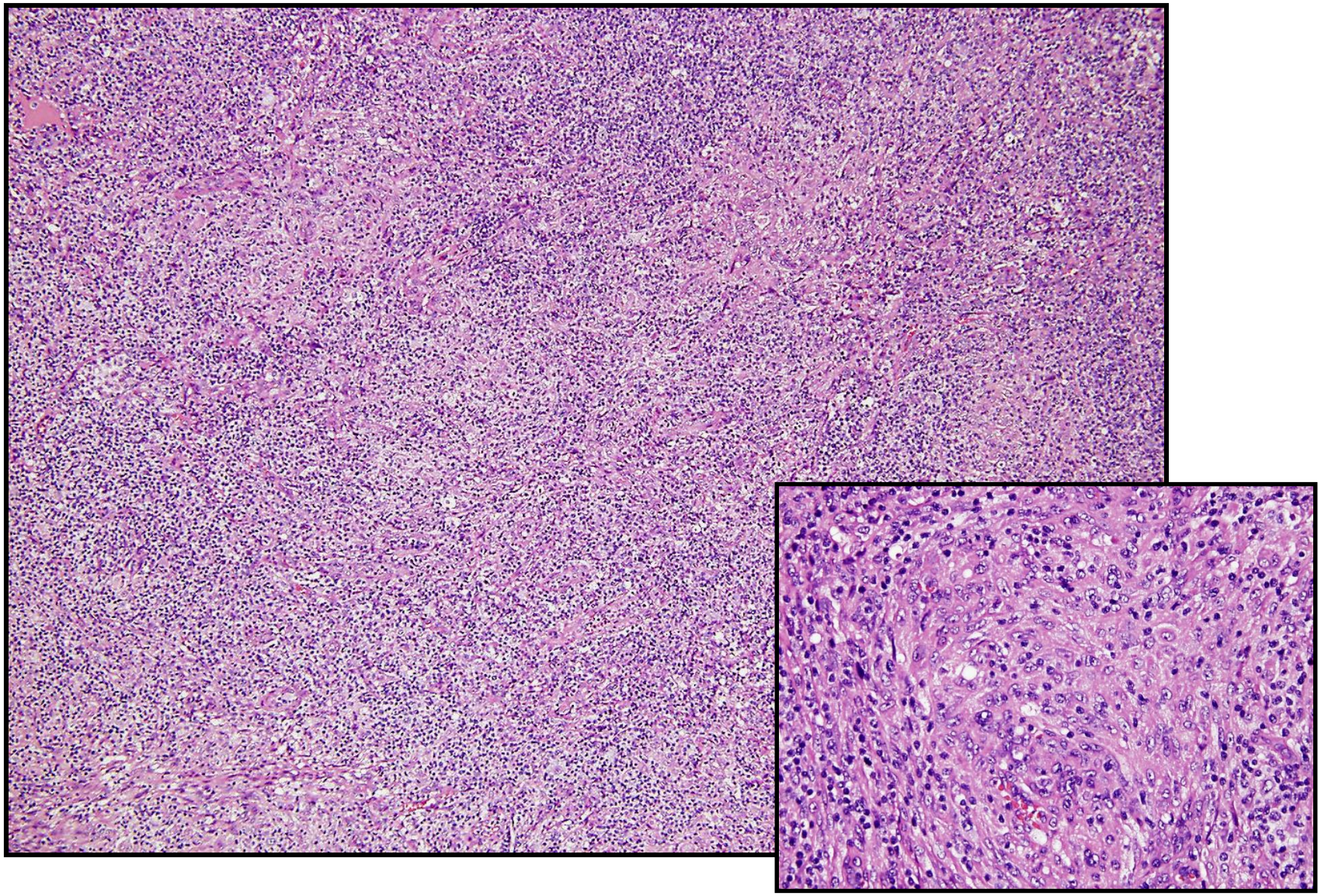
Angioimmunoblastic T-cell Lymphoma

Pattern II



Angioimmunoblastic T-cell Lymphoma

Pattern III



Angioimmunoblastic T-cell Lymphoma

Histologic Features

Polymorphous infiltrate

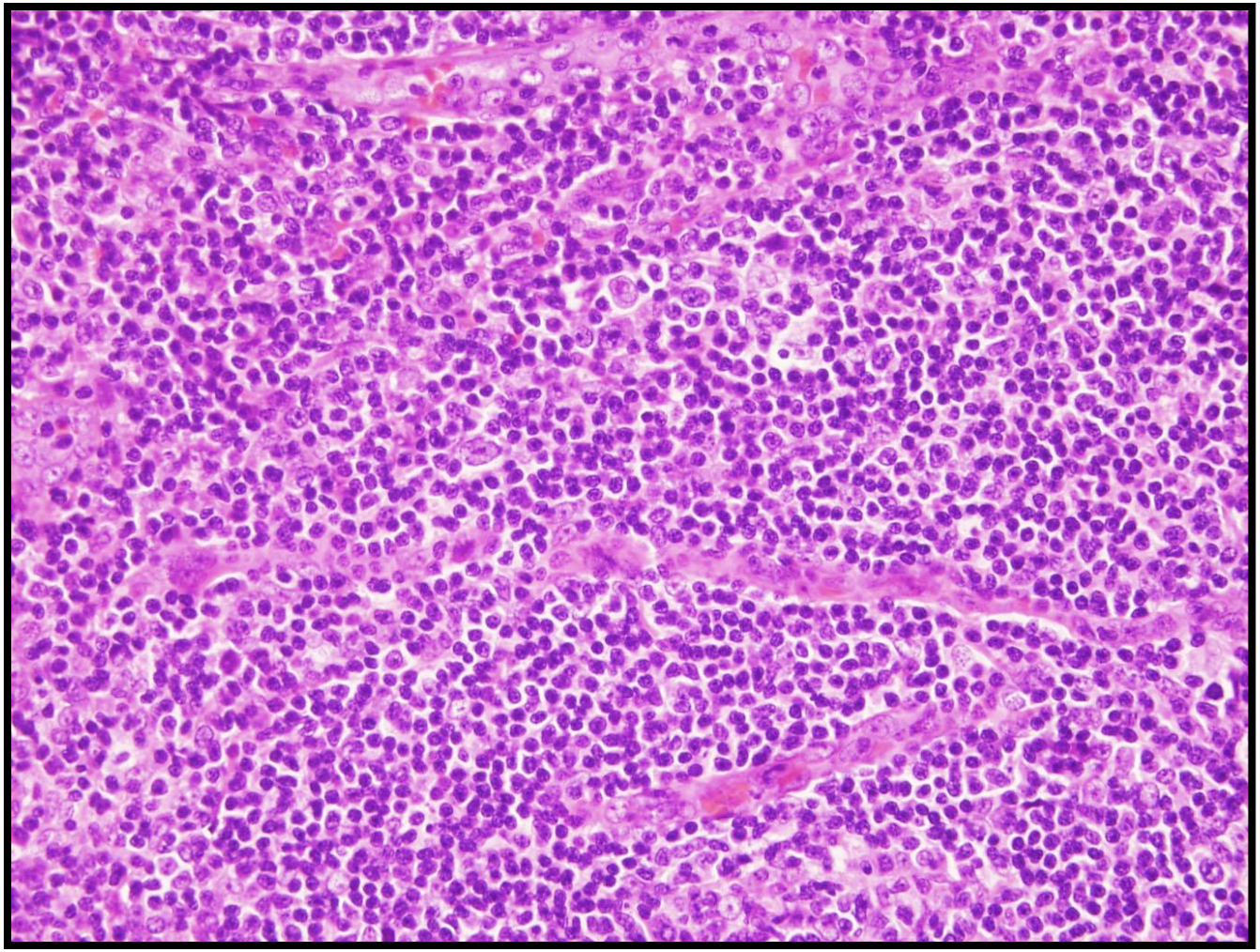
- **Small and larger lymphocytes**
- **Plasma cells**
- **Eosinophils**
- **Neoplastic (clear) cells**

Arborizing blood vessels (HEV)

Eosinophilic sludge - / +

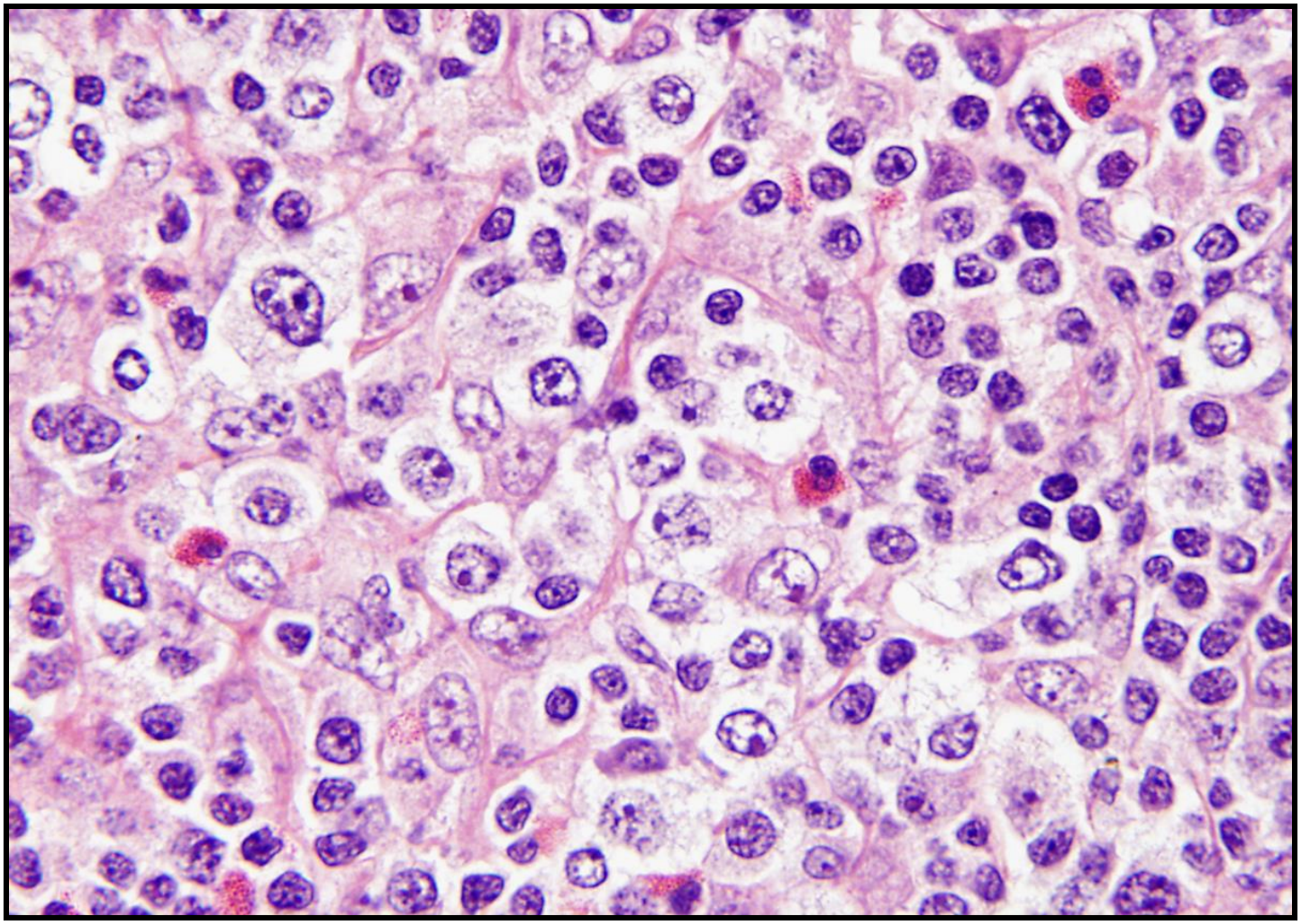
Angioimmunoblastic T-cell Lymphoma

High Endothelial Vessel proliferation



Angioimmunoblastic T-cell Lymphoma

Clusters of Clear Cells



Angioimmunoblastic T-cell Lymphoma

Differential Dx with PTCL-NOS

Morphological feature	AITL (n=48)	PTCL, NOS (n=81)	p Value†
Radiating FDCs (CD21+)	48/48 (100)	0/81 (0.0)	0.000
Marked proliferation of HEVs	46/48 (95.8)	28/81 (34.6)	0.000
Perinodal spread to fat	32/48 (66.7)	55/81 (67.9)	0.885
Immunoblasts, many (CD20+)	27/48 (56.3)	19/81 (23.5)	0.000
Plasma cells, many	26/48 (54.2)	20/81 (24.7)	0.001
Clear neoplastic cell clusters	25/48 (52.1)	21/81 (25.9)	0.003
Marked lymphocytic atypia	20/48 (41.7)	57/81 (70.4)	0.001
Eosinophils, many	18/48 (37.5)	22/81 (27.2)	0.220
Remnant germinal centre	5/48 (10.4)	8/81 (9.9)	1.000
Necrosis	4/48 (8.3)	7/81 (8.6)	1.000
Epithelioid cell clusters	3/48 (6.3)	10/81 (12.3)	0.418

+, chi square test

J Clin Pathol 64: 319, 2011

Angioimmunoblastic T-cell Lymphoma

Immunohistologic Features

Pan T-cell antigens +

May show aberrant loss of markers

T-follicular helper cell markers

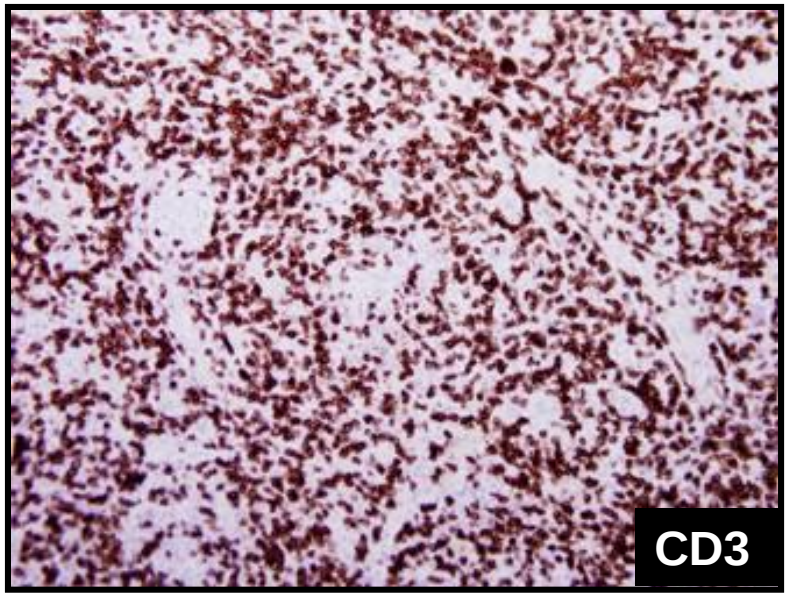
CD4	**+**
CXCL13	**+ / -**
CD10	**+ / -**
BCL-6	**+ / -**
PD-1	**+ / -**
ICOS	**+ / -**

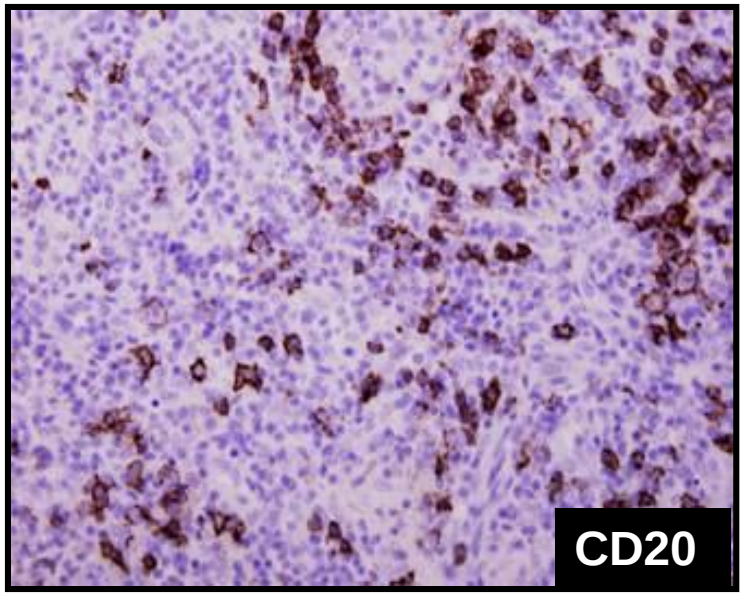
Increased dendritic cells (CD21+, CD23+)

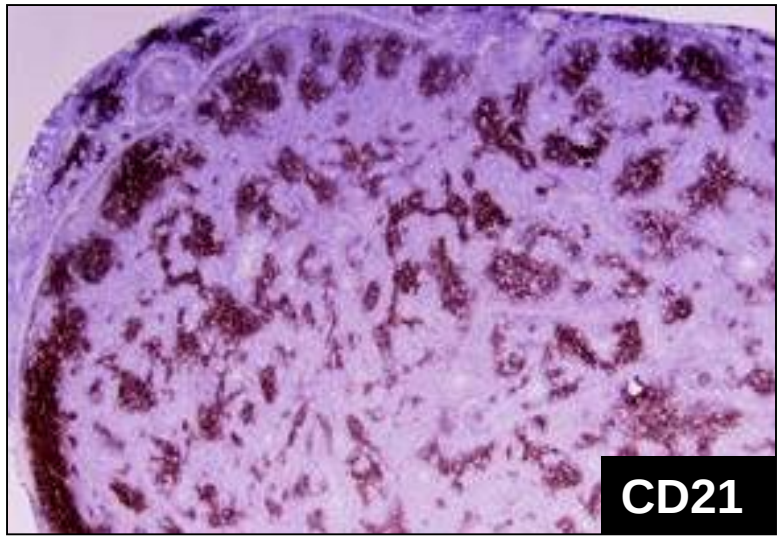
Scattered large CD20+ cells common

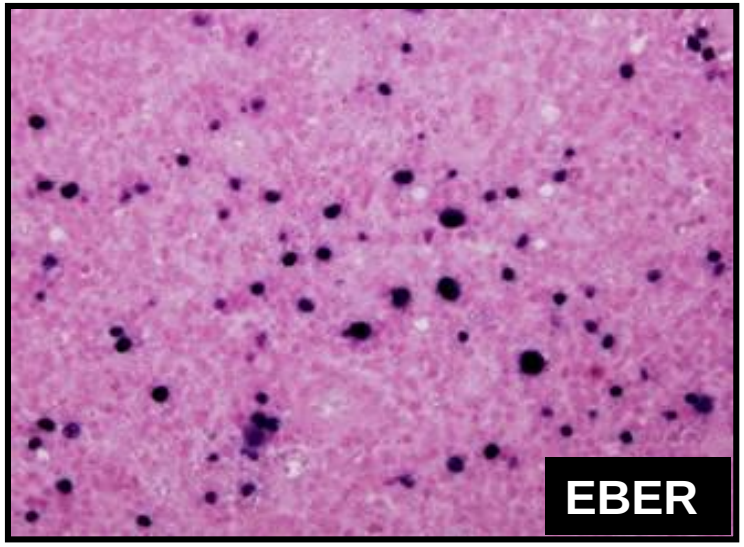
EBER+ (50-80%)

Angioimmunoblastic T-cell Lymphoma









Angioimmunoblastic T-cell Lymphoma
Molecular Features

80-90% **T-cell receptor gene rearrangements**

40-50% ***IGH*** **rearrangements**

90% **Cytogenetic abnormalities**

Trisomy 3, 5, or X

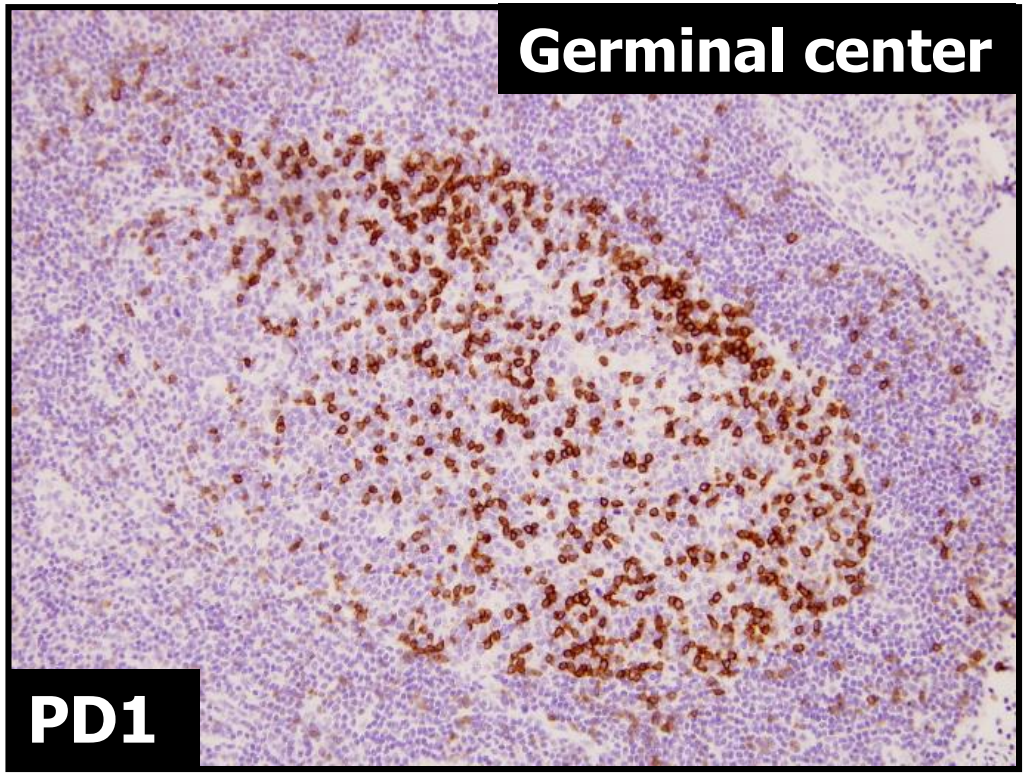
Gene expression profile

Follicular T helper cell

GEP Studies have shown that AITL arises from T-follicular helper cells (TFH) of GC

TFH cells interact with GC B cells and promote survival, IG class switch and somatic mutation

TFH cells suppress T-cell immunity

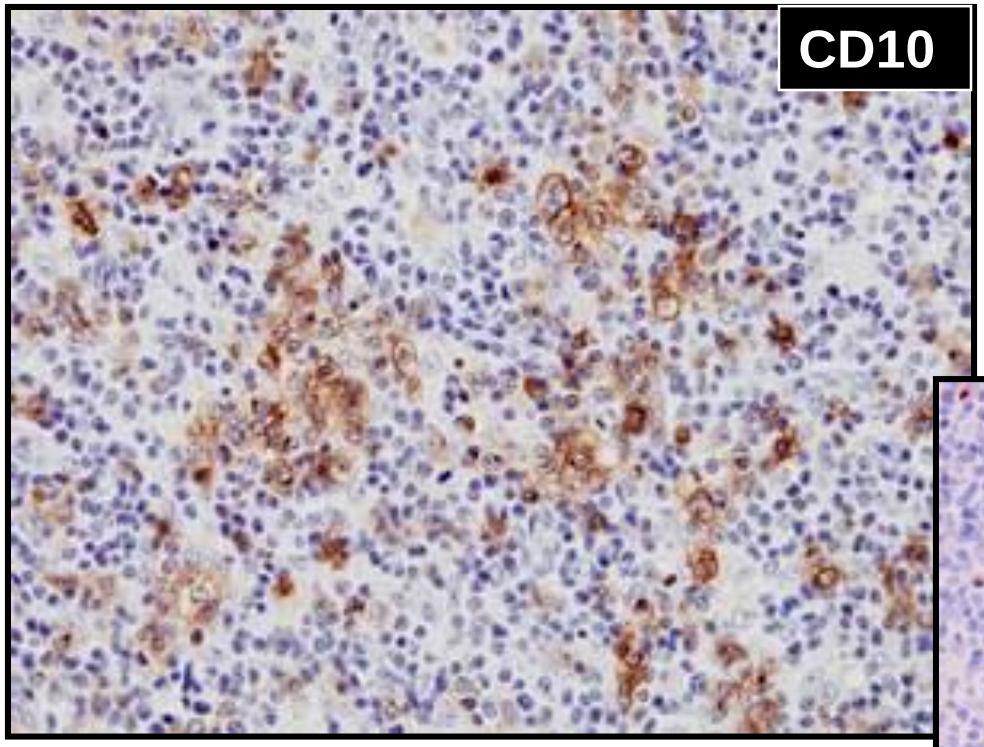


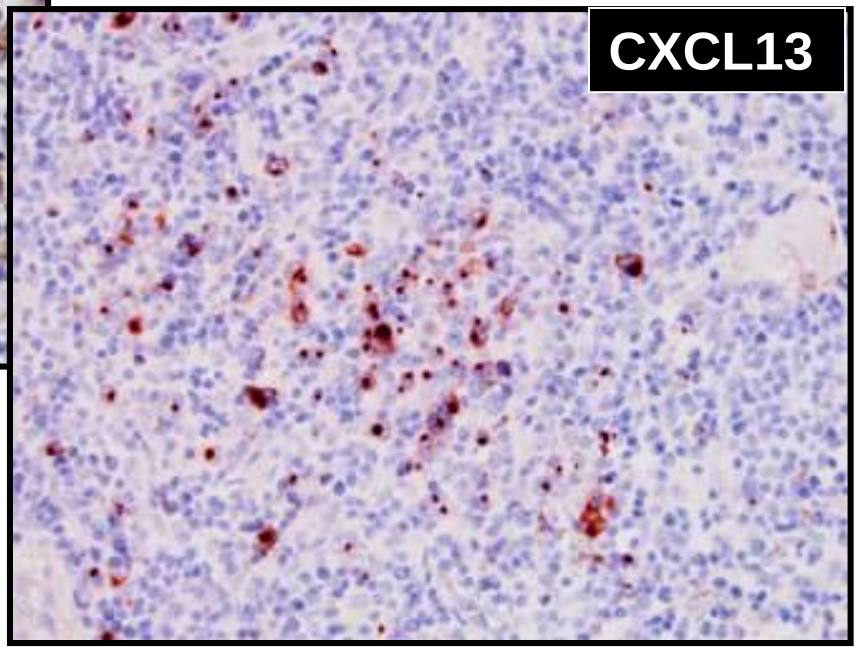
TFH cells express

- CD10
- BCL6
- PD1
- CXCL13
- ICOS
- CD57
- CD28
- CD40L
- IL-21

Angioimmunoblastic T-cell Lymphoma

Tumor of T Follicular Helper (TFH) Cells





Angioimmunoblastic T-cell Lymphoma
Specificity of TFH Markers

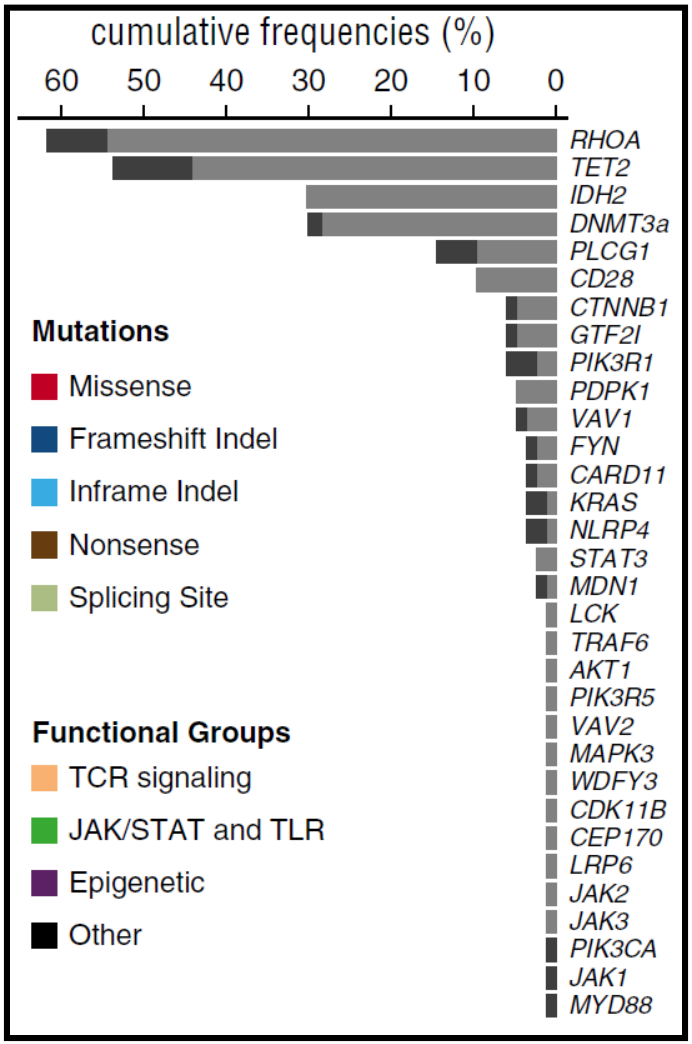
Lymphoma Type	CD10	BCL6	PD-1	CXCL13
AITL	75.0	66.7	93.8	97.9
PTCL, NOS	9.9	8.6	17.3	21.0
ALCL, ALK-	0.0	28.6	7.1	7.1
ALCL, ALK+	0.0	68.4	0.0	0.0
NK/TCL	0.0	27.3	0.0	54.5
T-LBL	27.3	9.1	0.0	0.0

J Clin Pathol 64: 319, 2011

Angioimmunoblastic T-cell Lymphoma

Recurrent Mutations shown by NGS

RHOA	60%
TET2	52%
IDH2	30%
DNMT3A	29%
PLCG1	14%
CD28	~9%
CTNNB1	~6%
GTF2I	~6%
PI3K	~6%
VAV1	~5%
FYN	~4%
CARD11	~3%



Blood 128: 1490, 2016

Angioimmunoblastic T-cell Lymphoma
Recurrent Mutations

RHOA

Involved in actin cytoskeleton
Downstream of T-cell receptor activation

TET2, IDH2, DNMT3A

Epigenetic modification

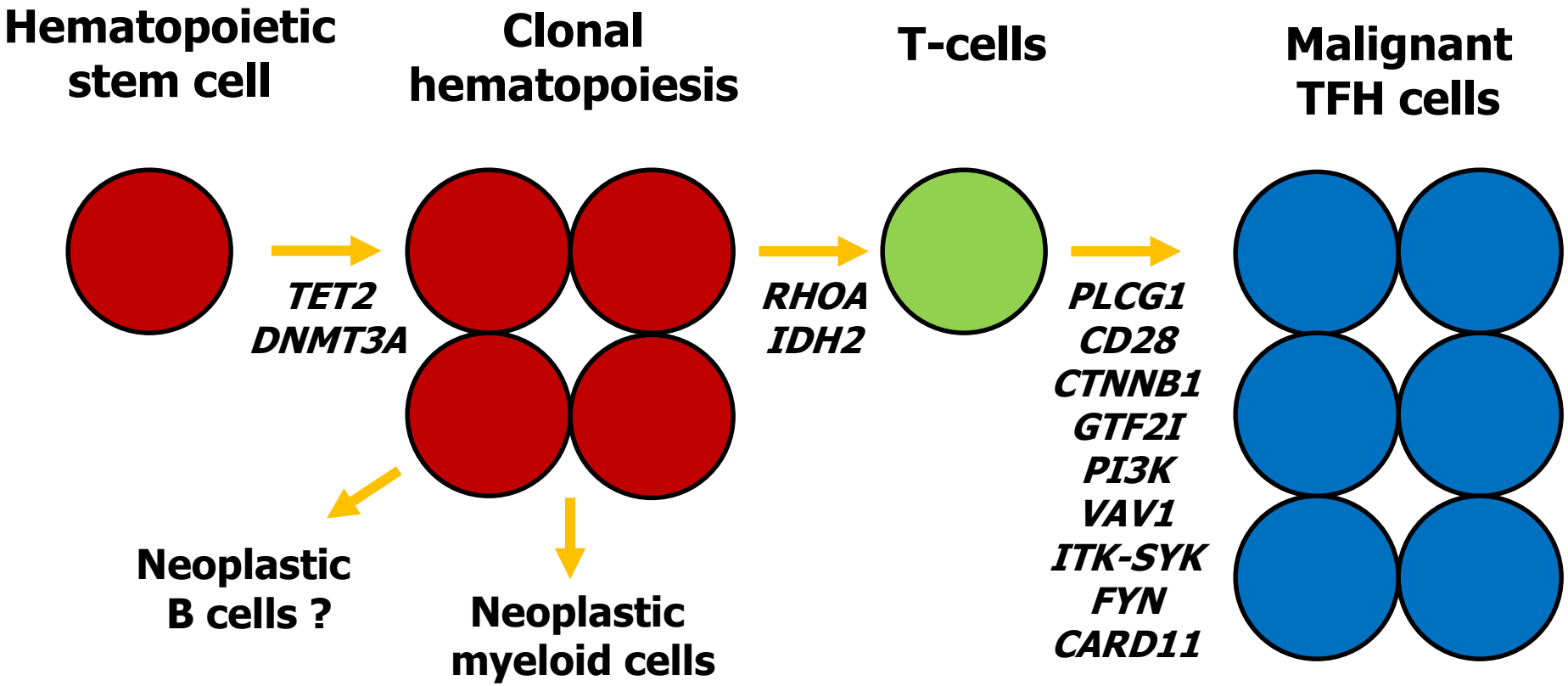
PLCG1, CD28, CTNNB1, GTF2I, PI3K

T-cell receptor activation

Blood 128: 1490, 2016

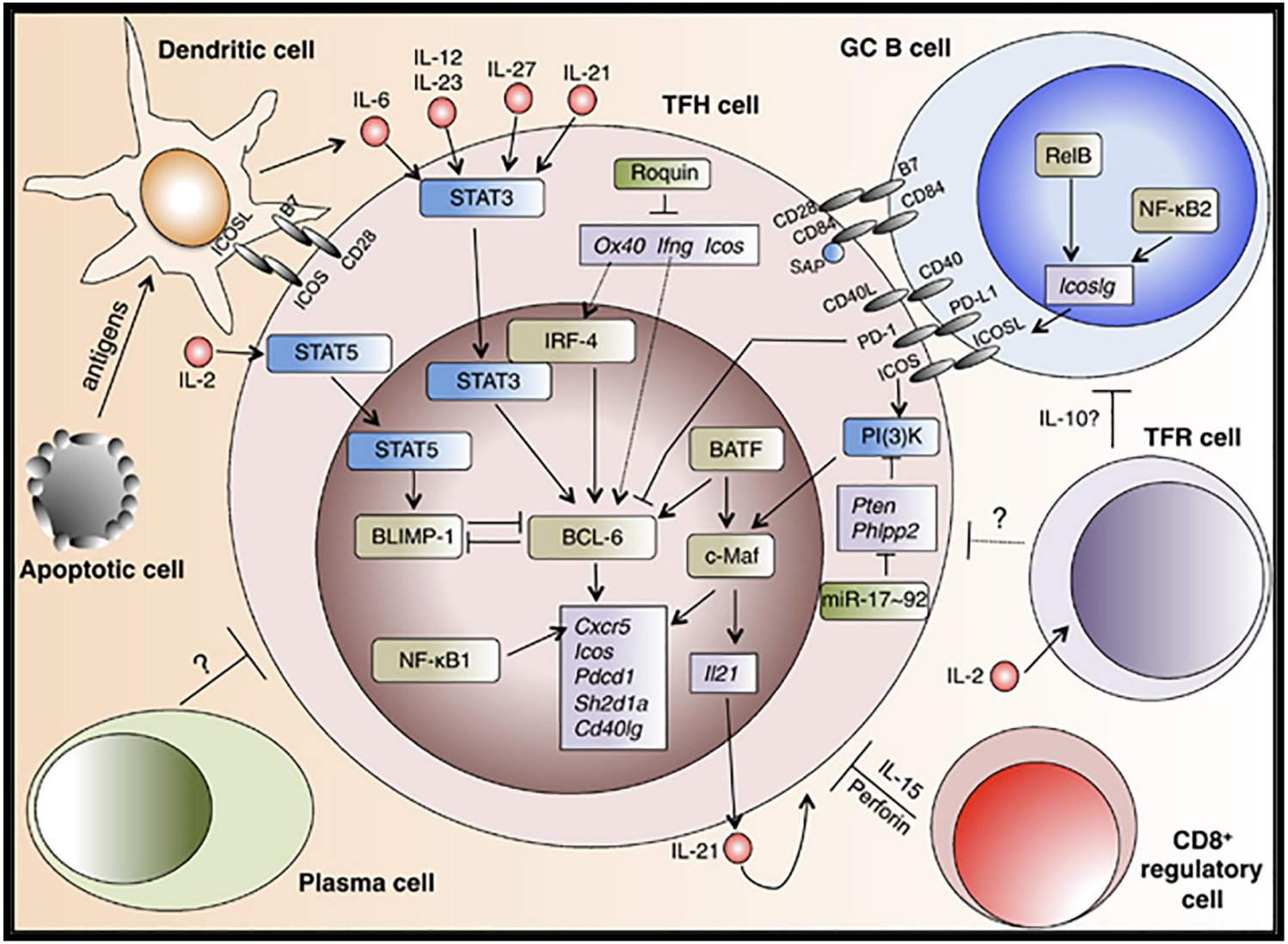
Angioimmunoblastic T-cell Lymphoma

Multistep Genetic Pathogenesis



modified from Int J Clin Exp Pathol 14: 1108, 2021

What do TFH Cells Do?



Immunol Cell Biol 92: 40, 2014

Angioimmunoblastic T-cell Lymphoma
Differential Diagnosis

Reactive follicular hyperplasia

Castleman disease, hyaline vascular variant

Granulomatous lymphadenitis

Marginal zone lymphoma

Diffuse large B-cell lymphoma

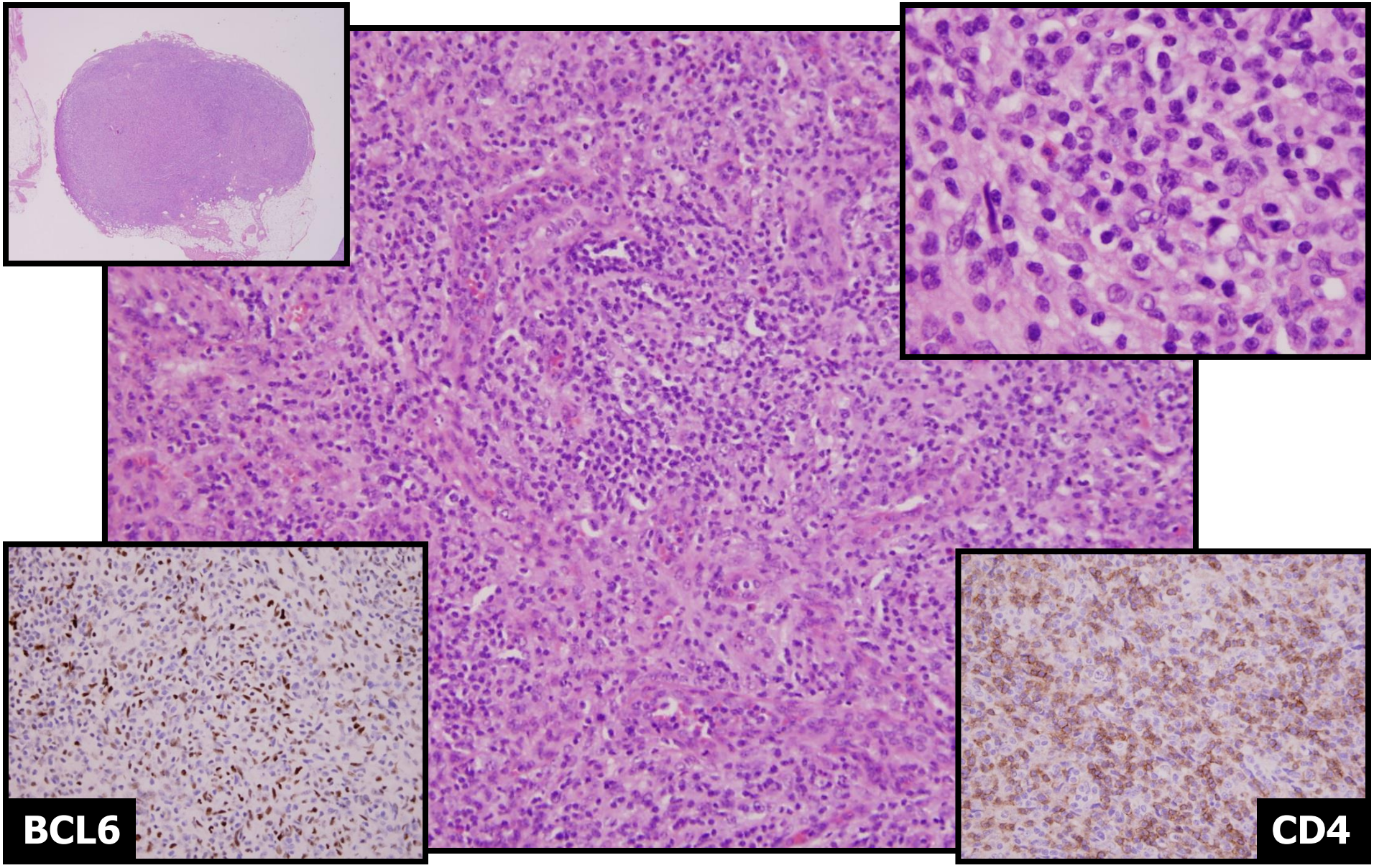
Plasmacytoma

Classic Hodgkin lymphoma

Mycosis fungoides involving lymph node

PTCL with TFH immunophenotype

Peripheral T-cell Lymphoma with a TFH Immunophenotype



Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma

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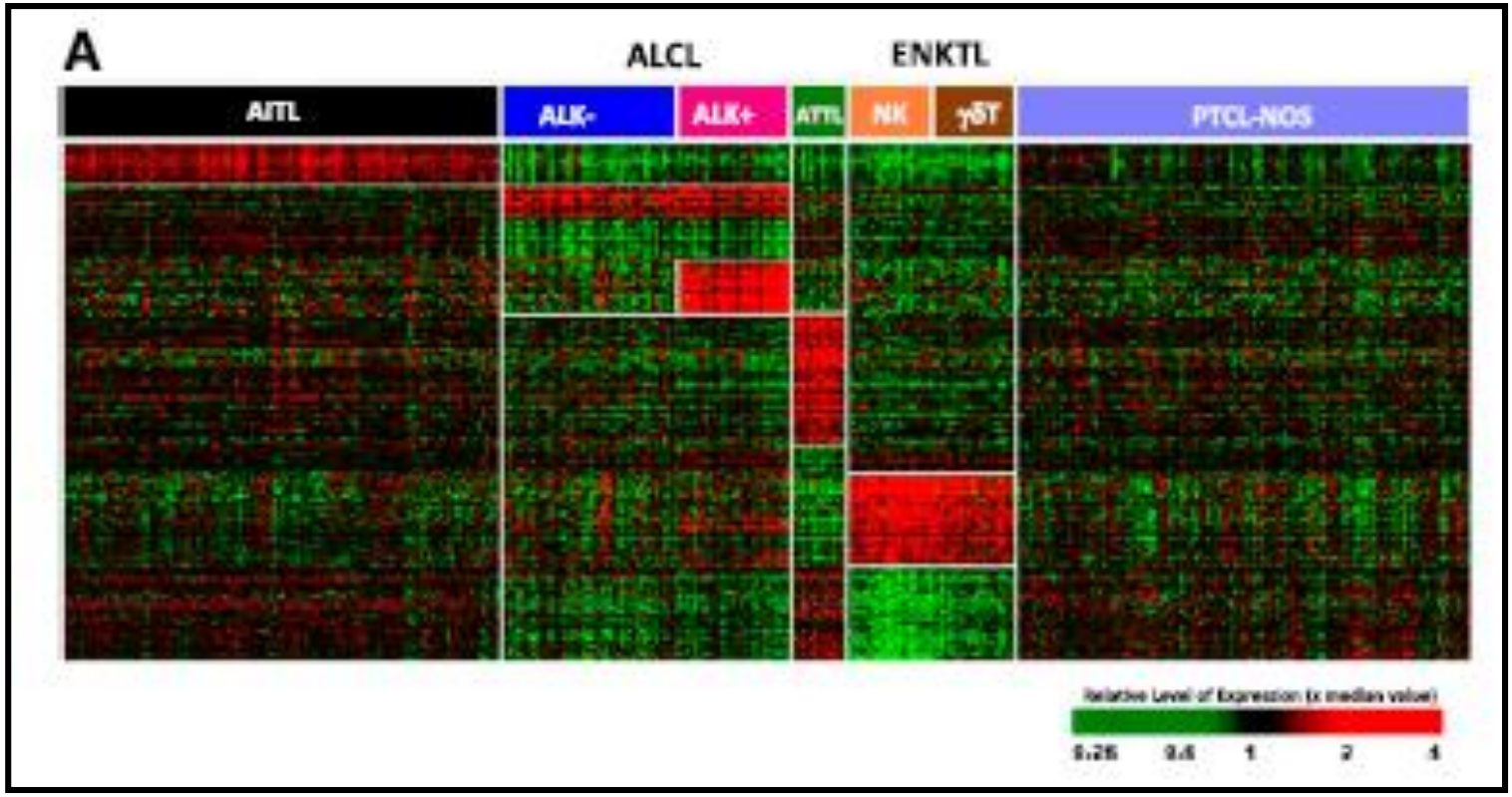
GEP was performed on 372 T-cell lymphomas



Blood 123: 2915, 2014

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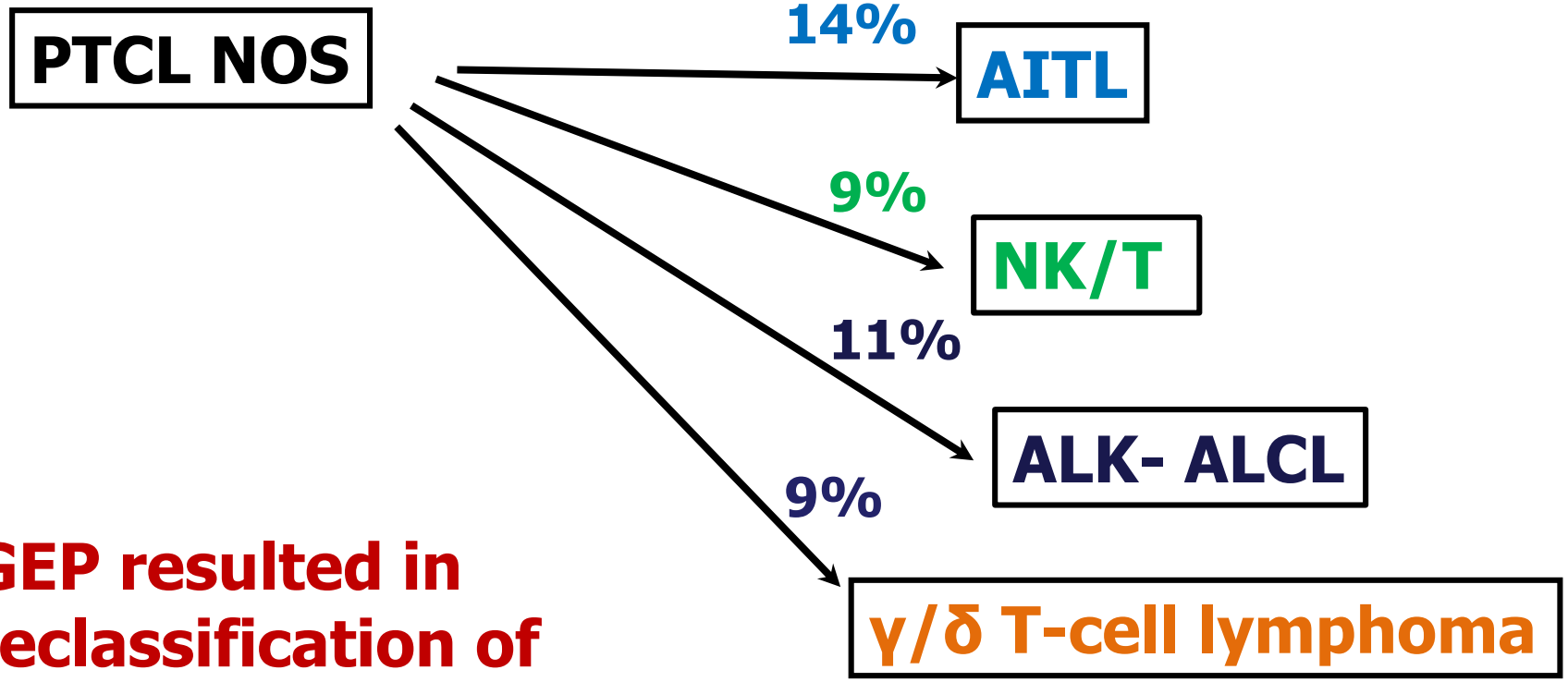


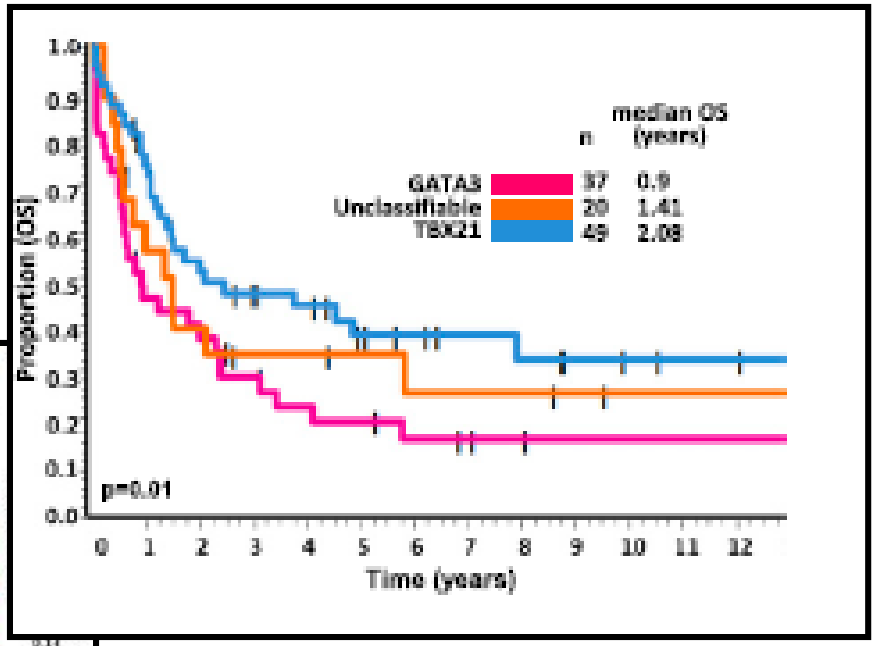
GEP resulted in reclassification of PTCL NOS

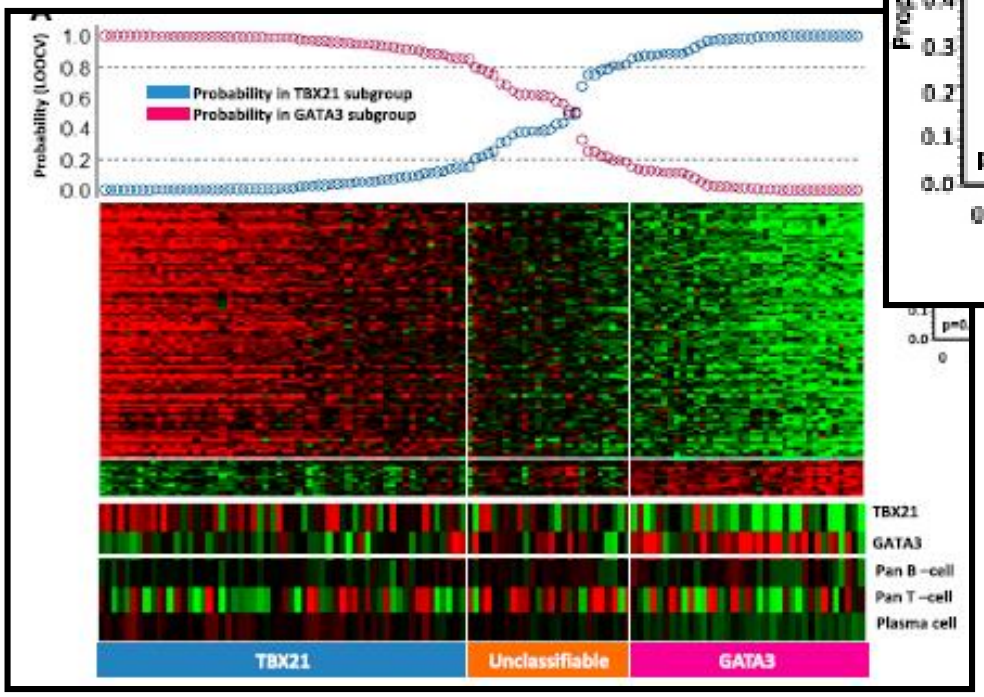
Blood 123: 2915, 2014

Gene Expression Profiling of PTCL NOS

GATA3 and TBX21 (T-bet) Subsets

GATA3 type has a poorer prognosis





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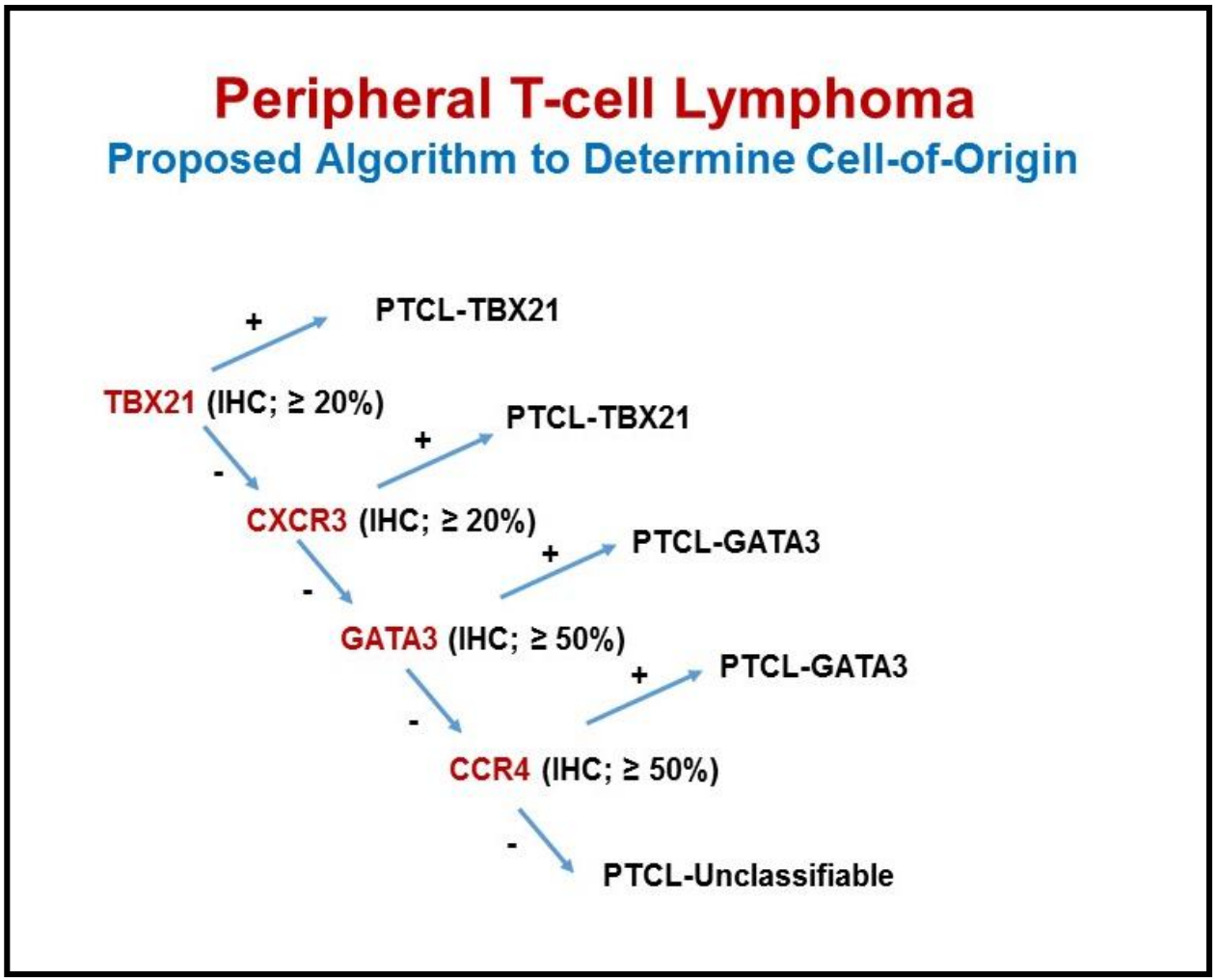
Probably Coming to You Soon



Amador C et al. Blood 134: 2159, 2019