**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

# Protocol for the Examination of Precursor and Mature Lymphoid Malignancies

**Version:** 1.0.0.0
**Protocol Posting Date:** September 2023
The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.
This protocol applies to precursor and mature lymphoid malignancies involving blood, bone marrow, lymph node, cutaneous, extranodal/mucosal, or any other anatomic site.
**The following tumor types should be reported using this protocol:**

| Tumor Type |
|---|
| B-lymphoblastic leukemia / lymphomas |
| +Pre-neoplastic lymphoid proliferations (optionally reported) including monoclonal B lymphocytosis |
| Mature B-cell neoplasms including: Follicular neoplasms, Mantle cell neoplasms, Lymphoplasmacytic lymphoma, Marginal zone lymphomas, Splenic B-cell lymphomas / leukemias, Large B-cell lymphomas, KSHV / HHV8-associated B-cell lymphoid proliferations and lymphomas, other mature B-cell neoplasms |
| Hodgkin lymphomas |
| Precursor T-cell neoplasms |
| Mature T-cell and NK-cell leukemias including: Primary cutaneous T-cell lymphoid proliferations and lymphomas, Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas, Hepatosplenic T-cell lymphoma, Anaplastic large cell lymphomas, Nodal T-follicular helper (TFH) cell lymphomas, Peripheral T-cell lymphoma, NOS |
| EBV-positive NK / T-cell lymphomas |
| EBV-positive T-cell and NK-cell lymphoid proliferations and lymphomas of childhood |
| Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation |

**The following tumor types should NOT be reported using this protocol:**

| Tumor Type |
|---|
| Myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangement, Acute leukemias of mixed or ambiguous lineage, plasmacytoid dendritic cell neoplasms (use Myeloid and Mixed/Ambiguous Lineage Neoplasms) |
| Plasma cell neoplasms, Immunoglobulin-related (AL) amyloidosis, Monoclonal immunoglobulin deposition disease, Heavy chain disease (use Plasma Cell Malignancies and Immunoglobulin Deposition Related Disorders) |

## TUMOR

**Site(s) of Tumor Involvement in Sample (Note A) (select all that apply)**
___ Bone marrow (specify percent involvement of neoplastic cells): _____ %
___ Blood (specify percent involvement of neoplastic cells): _____ %
___ Anterior mediastinum
___ Lymph node
___ Cutaneous
___ Extranodal / mucosal site
___ Other (specify): _____

**Molecular Alterations Detected# (select all that apply)**
*# Select all those with significant mutations*
___ ALK translocation (specify): _____
___ MALT1 translocation (specify): _____
___ ATM mutation (specify): _____
___ B2M mutation (specify): _____

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

___ BCL10 translocation (specify): _____
___ BIRC3 mutation (specify): _____
___ BTK mutation (specify): _____
___ CARD11 mutation (specify): _____
___ CD79A / B mutation (specify): _____
___ BCR::ABL1 p190 fusion transcript
___ BCR::ABL1 p210 fusion transcript
___ BCR::ABL1, unspecified transcript
___ BCL2 mutation (specify): _____
___ BCL2 translocation (specify): _____
___ BCL6 mutation (specify): _____
___ BCL6 translocation (specify): _____
___ BRAF mutation (specify): _____
___ CDKN2A / 2B mutation (specify): _____
___ CCND1 (Cyclin D1) translocation (specify): _____
___ CCND2 (Cyclin D2) translocation (specify): _____
___ CCND3 (Cyclin D3) translocation (specify): _____
___ CXCR4 mutation (specify): _____
___ DUSP22 translocation (specify): _____
___ DNMT3A mutation (specify): _____
___ ETV6 mutation (specify): _____
___ ETV6::RUNX1 fusion (specify): _____
___ EZH2 mutation (specify): _____
___ FBXW7 mutation (specify): _____
___ GATA3 mutation (specify): _____
___ iAMP21 (specify): _____
___ IDH1 / 2 mutation (specify): _____
___ IGH::IL3 rearrangement (specify): _____
___ IGHV mutated (specify): _____
___ IGHV unmutated (specify): _____
___ IRF4 mutation (specify): _____
___ JAK1 mutation (specify): _____
___ JAK2 mutation (specify): _____
___ JAK3 mutation (specify): _____
___ KLKF2 mutation (specify): _____
___ KRAS mutation (specify): _____
___ KMT2A rearrangement (specify): _____
___ MYC rearrangement (specify): _____
___ MYD88 mutation (specify): _____
___ NOTCH1 mutation (specify): _____
___ NOTCH2 mutation (specify): _____
___ NRAS mutation (specify): _____
___ PDGFRA translocation (specify): _____
___ PLCG1 / 2 mutation (specify): _____
___ PTEN mutation (specify): _____
___ RB1 mutation (specify): _____
___ RHOA mutation (specify): _____
___ RPS15 mutation (specify): _____
___ SF3B1 mutation (specify): _____
___ STAT3 mutation (specify): _____
___ STAT5B mutation (specify): _____
___ STAT6 mutation (specify): _____

___ TET2 mutation (specify): _____
___ TCF3::PBX1 rearrangement (specify): _____
___ TCF3::HLF fusion rearrangement (specify): _____
___ TNFAIP3 mutation (specify): _____
___ TNFRSF14 mutation (specify): _____
___ TP53 mutation (specify): _____
___ TP63 translocation (specify): _____
___ TRAF3 mutation (specify): _____
___ XPO1 mutation (specify): _____
___ Other alterations detected (specify): _____
___ Pending: _____

**Final Integrated Diagnosis (Note B)**

___ Precursor B-cell neoplasms

*B-lymphoblastic leukemia / lymphomas*

___ B-lymphoblastic leukemia / lymphoma, NOS
___ B-lymphoblastic leukemia / lymphoma with high hyperdiploidy
___ B-lymphoblastic leukemia / lymphoma with hypodiploidy
___ B-lymphoblastic leukemia / lymphoma with iAMP21
___ B-lymphoblastic leukemia / lymphoma with BCR::ABL1 fusion
___ B-lymphoblastic leukemia / lymphoma with BCR::ABL1-like features
___ B-lymphoblastic leukemia / lymphoma with KMT2A rearrangement
___ B-lymphoblastic leukemia / lymphoma with ETV6::RUNX1 fusion
___ B-lymphoblastic leukemia / lymphoma with ETV6::RUNX1-like features
___ B-lymphoblastic leukemia / lymphoma with TCF3::PBX1 fusion
___ B-lymphoblastic leukemia / lymphoma with IGH::IL3 fusion
___ B-lymphoblastic leukemia / lymphoma with TCF3::HLF fusion
___ B-lymphoblastic leukemia / lymphoma with other defined genetic alterations

*Other precursor B-cell neoplasm*

___ B-lymphoblastic leukemia / lymphoma, pending additional studies (specify): _____

___ Mature B-cell neoplasms

*Pre-neoplastic lymphoid proliferations (optionally reported)*

+___ Monoclonal B-cell lymphocytosis, CLL-type, low-count (specify absolute count of clonal cells, if possible) (x 10*9/L): _____ x 10*9/L
+___ Monoclonal B-cell lymphocytosis, CLL-type (specify absolute count of clonal cells, if possible) (x 10*9/L): _____ x 10*9/L
+___ Monoclonal B-cell lymphocytosis, non-CLL type (specify absolute count of clonal cells, if possible) (x 10*9/L) : _____ x 10*9/L

*CLL / SLL*

___ Chronic lymphocytic leukemia / small lymphocytic lymphoma

*Follicular neoplasms*
___ In situ follicular B-cell neoplasm
___ Follicular lymphoma, classic type (cFL)
___ Follicular lymphoma with unusual cytologic features (uFL)
___ Follicular lymphoma with predominantly diffuse growth pattern (dFL)
___ Follicular large B-cell lymphoma
___ Pediatric-type follicular lymphoma
___ Duodenal-type follicular lymphoma
___ Primary cutaneous follicle center lymphoma
*Mantle cell neoplasms*
___ In situ mantle cell neoplasm
___ Mantle cell lymphoma
___ Leukemic non-nodal mantle cell lymphoma
*Lymphoplasmacytic lymphoma*
___ Lymphoplasmacytic lymphoma
*Marginal zone lymphomas*
___ Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
___ Primary cutaneous marginal zone lymphoma
___ Nodal marginal zone lymphoma
___ Pediatric nodal marginal zone lymphoma
*Splenic B-cell lymphomas / leukemias*
___ Hairy cell leukemia
___ Splenic marginal zone lymphoma
___ Splenic diffuse red pulp small B-cell lymphoma
___ Splenic B-cell lymphoma / leukemia with prominent nucleoli
*Large B-cell lymphomas*
___ Diffuse large B-cell lymphoma, NOS
___ T-cell / histiocyte-rich large B-cell lymphoma
___ Diffuse large B-cell lymphoma / high grade B-cell lymphoma with MYC and BCL2 rearrangements
___ ALK-positive large B-cell lymphoma
___ Large B-cell lymphoma with IRF4 rearrangement
___ High grade B-cell lymphoma with 11q aberrations
___ Lymphomatoid granulomatosis
___ EBV-positive diffuse large B-cell lymphoma
___ Diffuse large B-cell lymphoma associated with chronic inflammation
___ Fibrin-associated large B-cell lymphoma
___ Fluid overload-associated large B-cell lymphoma
___ Plasmablastic lymphoma
___ Primary large B-cell lymphoma of immune-privileged sites
___ Primary cutaneous diffuse large B-cell lymphoma, leg type
___ Intravascular large B-cell lymphoma
___ Primary mediastinal large B-cell lymphoma
___ Mediastinal grey zone lymphoma
___ High-grade B-cell lymphoma, NOS
___ Burkitt lymphoma
*KSHV / HHV8-associated B-cell lymphoid proliferations and lymphomas*
___ Primary effusion lymphoma
___ KSHV / HHV8-positive diffuse large B-cell lymphoma
___ KSHV / HHV8-positive germinotropic lymphoproliferative disorder
*Hodgkin lymphomas*
___ Classic Hodgkin lymphoma
___ Nodular lymphocyte predominant Hodgkin lymphoma
*Other mature B-cell neoplasm*
___ Mature B-cell neoplasm (specify): _____

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

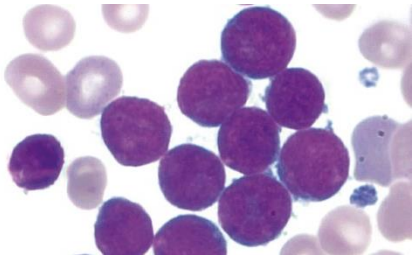
___ Precursor T-cell neoplasms
  ___ T-lymphoblastic leukemia / lymphoma, NOS
  ___ Early T-precursor lymphoblastic leukemia / lymphoma
  ___ Precursor T-cell neoplasm, pending additional studies (specify): _____
___ Mature T-cell and NK-cell neoplasms
  *Mature T-cell and NK-cell leukemias*
  ___ T-prolymphocytic leukemia
  ___ T-large granular lymphocytic leukemia
  ___ NK-large granular lymphocytic leukemia
  ___ Adult T-cell leukemia / lymphoma
  ___ Sezary syndrome
  ___ Aggressive NK-cell leukemia
  *Primary cutaneous T-cell lymphoid proliferations and lymphomas*
  ___ Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder
  ___ Primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder
  ___ Mycosis fungoides
  ___ Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Lymphomatoid papulosis
  ___ Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: 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
  ___ Primary cutaneous peripheral T-cell lymphoma, NOS
  *Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas*
  ___ Indolent T-cell lymphoma of the gastrointestinal tract
  ___ Indolent NK-cell lymphoproliferative disorder 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 lymphomas*
  ___ ALK-positive anaplastic large cell lymphoma
  ___ ALK-negative anaplastic large cell lymphoma
  ___ Breast implant-associated anaplastic large cell lymphoma
  *Nodal T-follicular helper (TFH) cell lymphomas*
  ___ Nodal TFH cell lymphoma, angioimmunoblastic-type
  ___ Nodal TFH cell lymphoma, follicular-type
  ___ Nodal TFH cell lymphoma, NOS
  *Other peripheral T-cell lymphoma*
  ___ Peripheral T-cell lymphoma, NOS
  *EBV-positive NK / T-cell lymphomas*
  ___ EBV-positive NK-cell and T-cell lymphoma
  ___ EBV-positive nodal T- and NK-cell lymphoma
  ___ Extranodal NK / T-cell lymphoma
  *EBV-positive T-cell and NK-cell lymphoid proliferations and lymphomas of childhood*
  ___ Severe mosquito bite allergy
  ___ Hydroa vacciniforme lymphoproliferative disorder
  ___ Systemic chronic active EBV disease
  ___ Systemic EBV-positive T-cell lymphoma of childhood
  *Other mature T- or NK-cell neoplasm*
  ___ Mature T- or NK-cell neoplasm (specify): _____
___ Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation
  ___ Hyperplasias arising in immune deficiency / dysregulation

___ Polymorphic lymphoproliferative disorders arising in immune deficiency / dysregulation
___ EBV-positive mucocutaneous ulcer
___ Lymphomas arising in immune deficiency / dysregulation
___ Inborn error of immunity-associated lymphoid proliferations and lymphomas
**+Specify Name of Lesion:** _____
**+Specify Virus Status:** _____
**+Specify Type of Immunodeficiency:** _____

**+Possible Transformation from Indolent Lymphoma (Note C)**
___ Not applicable
___ No overt evidence of transformation from more indolent lymphoma / other lymphoma type
___ Lymphoma favored to represent transformation event from indolent lymphoma (explain):
_____

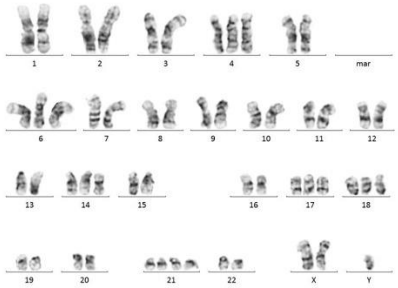
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## B-LYMPHOBLASTIC LEUKEMIA / LYMPHOMA, NOS



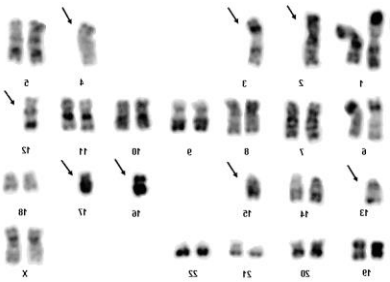
- B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL) is a neoplasm of precursor lymphoid cells committed to the B-cell lineage, involving bone marrow and usually peripheral blood
- Essential: meets the diagnostic criteria for B-ALL/LBL; does not meet criteria for any defined B-ALL/LBL types after comprehensive testing.

## B-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA WITH HIGH HYPERDIPLOIDY



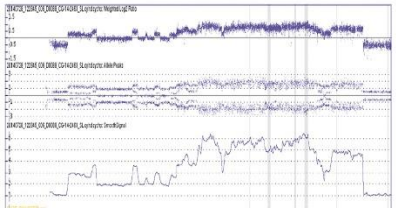
- B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL) with high hyperdiploidy is a neoplasm of lymphoblasts of B-cell lineage defined by a karyotype comprising 51–65 chromosomes, characterized by recurrent, non-random gains of one or more copies of entire chromosomes (usually the X chromosome and chromosomes 4, 6, 10, 14, 17, 18 and 21) in the absence of other type-defining gene fusions and rearrangements.

## B-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA WITH HYPODIPLOIDY



- Subtypes: Near-haploid B-ALL/LBL with hypodiploidy (24–31 chromosomes); low-hypodiploid B-ALL/LBL with hypodiploidy (32–39 chromosomes); high-hypodiploid B-ALL/LBL with hypodiploidy (40–43 chromosomes)
- Approximately 50% of children with low-hypodiploid B-ALL/LBL have germline TP53 variants (Li–Fraumeni syndrome), Additional mutations including RAS and IKZF2 deletions have also been identified.
- Essential: meets the diagnostic criteria for B-ALL/LBL (see section B-lymphoblastic leukaemia/lymphoma); demonstration of hypodiploidy (≤ 43 chromosomes) by karyotyping and/or FISH analysis.

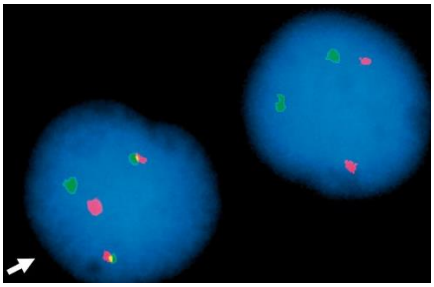
## B-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA WITH IAMP21



- B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL) with intrachromosomal amplification of chromosome 21 (iAMP21) and gross rearrangements involving the long arm of chromosome 21.
- evidence of iAMP21 as illustrated by the alternating copy-number changes across the entire chromosome, in addition to amplification across the RUNX1 locus and terminal copy-number loss
- Essential: meets the diagnostic criteria for B-ALL/LBL (see section B-lymphoblastic leukaemia/lymphoma); demonstration of a grossly abnormal chromosome 21 by karyotyping; demonstration of ≥ 5 copies of RUNX1 per cell, with ≥ 3 copies on a single abnormal chromosome 21 by karyotyping and FISH analysis.

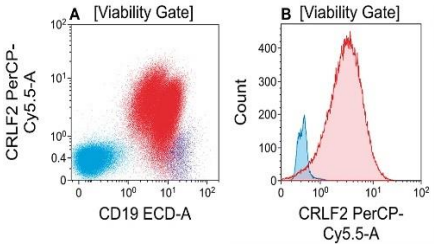
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## B-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA WITH BCR::ABL1 FUSION



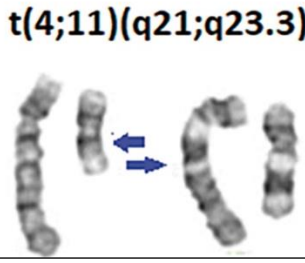
- B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL) with BCR::ABL1 fusion is a neoplasm of lymphoblasts of B lineage defined by the presence of a rearrangement between BCR on chromosome 22q11.2 and the oncogene ABL1 on chromosome 9q34.1.
- FISH shows: one red normal ABL1, one green normal BCR, and two BCR::ABL1 fusion signals indicating the 9;22 translocation
- Essential: meets the diagnostic criteria for B-ALL/LBL; demonstration of the BCR::ABL1 fusion; exclusion of cases of B-ALL in which BCR::ABL1 is acquired as a secondary event during treatment or follow-up; exclusion of B-lymphoid blast crisis of CML.

## B-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA WITH BCR::ABL1-LIKE FEATURES




- BCR::ABL1-like B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL) is a neoplasm of lymphoblasts of B-cell lineage defined by DNA alterations that induce a phenotype similar to that of BCR::ABL1-positive B-ALL but lack the pathognomonic BCR::ABL1 rearrangement.
- Essential: meets the diagnostic criteria for B-ALL/LBL (see section B-lymphoblastic leukaemia/lymphoma); demonstration of a BCR::ABL1-like gene expression signature and/or demonstration of major BCR::ABL1-like B-ALL/LBL-associated rearrangements. **CRLF2 is surrogate marker.**

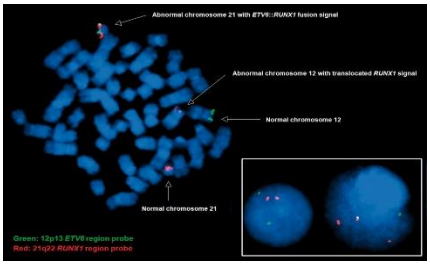
## B-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA WITH KMT2A REARRANGEMENT




Partial karyotype of chromosomes 4 and 11, indicating a t(4;11)(q21;q23.3) translocation

- B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL) with KMT2A rearrangement is a neoplasm of lymphoblasts of B-cell lineage defined by the presence of a rearrangement between KMT2A and one of the numerous fusion partners.
- BALL -KMT2A typically have a CD19+, CD34+, HLA-DR+; CD10−, CD24− immunophenotype and are often positive for the myeloid markers CD15 and CD65s, as well as the neural/glial antigen expression. **TDT negativity is also often seen.**
- Essential: meets the diagnostic criteria for B-ALL/LBL. demonstration of KMT2A rearrangement by FISH and/or RT-PCR and/or next-generation sequencing analysis.

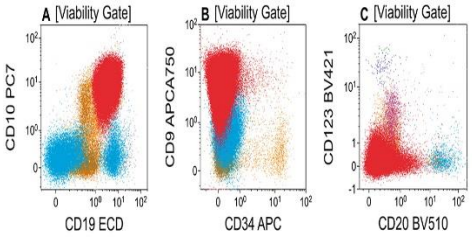
## B-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA WITH ETV6::RUNX1 FUSION, T(12:21)




- B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL) with ETV6::RUNX1 fusion is a neoplasm of lymphoblasts of B-cell lineage defined by the presence of rearrangement between ETV6 on chromosome 12p13.2 and RUNX1 on chromosome 21q22.1.
- ETV6::RUNX1 is the most common recurrent translocation in childhood B-ALL/LBL, 25% of B-ALL/LBL cases diagnosed in patients aged 2–10
- Essential: meets the diagnostic criteria for B-ALL/LBL; demonstration of ETV6::RUNX1 fusion. Favorable prognosis

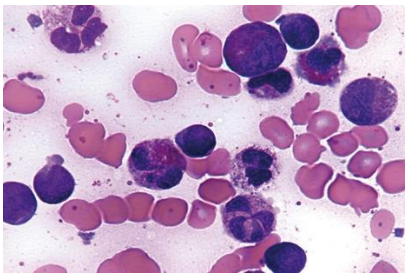
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## B-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA (B-ALL/LBL) WITH TCF3::PBX1 FUSION




- B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL) with TCF3::PBX1 fusion is a neoplasm of lymphoblasts of B-cell lineage defined by the presence of rearrangement between TCF3 on chromosome 19 and PBX1 on chromosome 1.
- Flow cytometry: Flow cytometry dot plots. B-ALL/LBL tumour cells (in red) show moderate CD19 and moderate CD10 expression (A), moderate CD9 but negative CD34 expression (B), and negative CD123 and negative CD20 expression (C).
- Essential: meets the diagnostic criteria for B-ALL/LBL; demonstration of TCF3::PBX1 rearrangement. Intermediate prognosis

## B-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA WITH IGH::IL3 FUSION

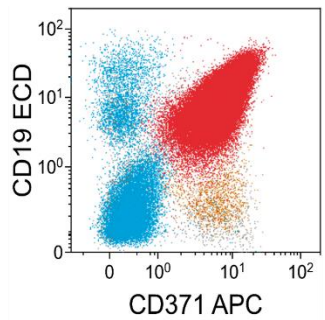


- B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL) with IGH::IL3 fusion is a neoplasm of lymphoblasts of B lineage defined by the juxtaposition of the IGH enhancer and the IL3 promoter, with characteristic peripheral blood and bone marrow eosinophilia.
- The lymphoblasts show typical expression of CD19 and CD10. A subset of cases shows expression of myeloid markers, CD33 and/or CD13. Both lymphoblasts and eosinophils express the IL-3 receptor, CD123
- Essential: meets the diagnostic criteria for B-ALL/LBL; demonstration of IGH::IL3 fusion. A small case series suggested an intermediate prognosis

## B-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA WITH TCF3::HLF FUSION

- New entity in 5th edition. B ALL with *TCF3::HLF* fusion (associated with aggressive behavior)

## B-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA WITH OTHER DEFINED GENETIC ALTERATIONS

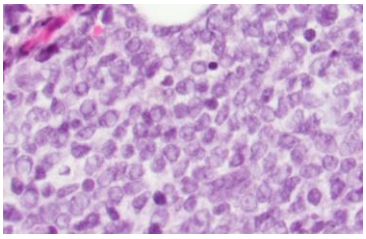



- Flow cytometric **DUX4-**rearrangement. **CD371** is expressed by leukaemic blasts (red) and normal granulocytes (brown), but not normal B cells or mature lymphocytes (blue).

- B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL) with other defined genetic abnormalities includes neoplasms of lymphoblasts of B-cell lineage defined by the presence of specific newly described or uncommon genetic drivers:
- lymphoblastic leukaemia with *DUX4*, MEF2D, ZNF384, PAX5, NUTM1, or MYC
- Essential: meets the general criteria for B-ALL/B-LBL; demonstration of a specific genetic abnormality as defined in this section; absence of genetic mutations of other B-ALL/LBL types. in adult B-ALL/LBL with MYC rearrangement, exclusion of diffuse large B-cell lymphoma / high-grade B-cell lymphoma with MYC and BCL2 rearrangements. DUX4 mutation best prognosis

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

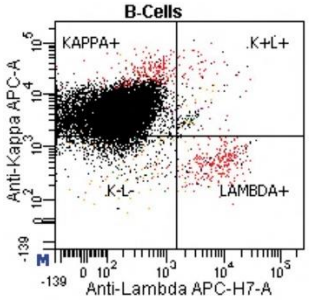
## B-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA NOS



- B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL) NOS is a neoplasm of lymphoblasts of B-cell lineage that includes B-ALL/LBL cases that do not meet the criteria for any B-ALL/LBL types that are defined by defined genetic abnormalities.
- Essential: meets the diagnostic criteria for B-ALL/LBL; does not meet criteria for any defined B-ALL/LBL types after comprehensive testing.
- In children, the prognosis of this group is intermediate.

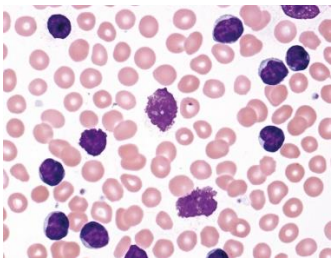
**Mature B-Cell neoplasm**

## MONOCLONAL B-CELL LYMPHOCYTOSIS




- Monoclonal B-cell lymphocytosis (MBL) is an asymptomatic condition characterized by the presence of a monoclonal B-cell population in the absence of lymphadenopathy, organomegaly, and any features diagnostic of another B-cell lymphoproliferative disorder (B-LPD).
- **Essential**: demonstration of a monoclonal B-cell population (light chain restriction or lack of surface light chain expression by flow cytometry, or monoclonal IG gene rearrangement with a peripheral B-cell count of < 5 × 109/L); absence of lymphadenopathy, organomegaly, and any features diagnostic of another B-LPD; for low-count MBL / clonal B-cell expansion: clonal B-cell count < 0.5 × 109/L and typical CLL/SLL phenotype; for CLL/SLL-type MBL: clonal B-cell count ≥ 0.5 × 109/L and typical CLL/SLL phenotype; for non–CLL/SLL-type MBL: any clonal B-cell expansion without the typical CLL/SLL phenotype.

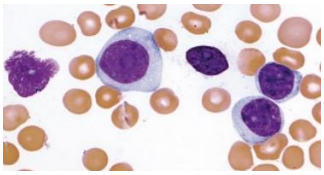
## CHRONIC LYMPHOCYTIC LEUKAEMIA / SMALL LYMPHOCYTIC LYMPHOMA



- CLL/SLL involves the peripheral blood, bone marrow, and lymphoid tissues such as lymph nodes, spleen, and tonsils. Less frequently, extranodal sites such as the liver, skin, CNS, kidney, pleura, and bones may be involved
- By flow cytometry, neoplastic cells are typically monotypic surface IgM dim+, IgD+/− (IgG+ in ~10% of cases), CD19+, CD5+, CD23+, CD43+, CD200+, CD20 dim+, CD11c variable, CD10−, CD79b−, FMC7−, CD25−, and CD103−, along with showing light chain restriction (dim expression)
- IHC: CD20 (positive/weak), CD5 (positive/weak), CD23 (variable), LEF1, CD43, IRF4 (MUM1 in the proliferation centers)
- Overexpression of ZAP70 (intracellular), CD38, and CD49d (membrane) and unmutated IGHV genes→ **poor prognosis**.
- Similarly, the presence of PCs in marrow biopsies is often associated with *TP53* abnormalities and complex karyotype .
- Among the serum parameters, B2M is an independent prognostic marker in early and advanced CLL/SLL. Elevated LDH appears to reflect an inferior prognosis in relapsed CLL/SLL
- Essential: Absolute monoclonal B-cell count ≥ 5 × 109/L

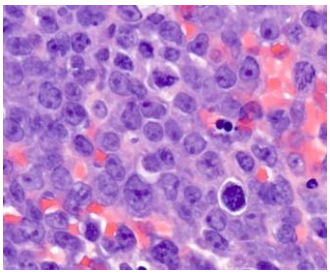
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

### ACCELERATED CLL/SLL



- It should be noted that cases with > 55% prolymphocytes, that have otherwise immunophenotypic features of CLL and that were classified as B-prolymphocytic leukaemia in the previous edition of the WHO, are now classified as prolymphocytic progression of CLL/SLL.
- Such cases often show TP53 disruption and have a clinical outcome between that of typical CLL/SLL and RT

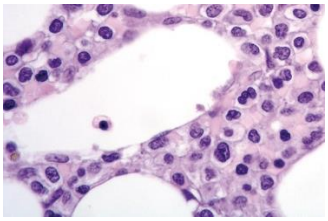
### RICHTER TRANSFORMATION



- Transformation of a chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) into an aggressive lymphoma, primarily diffuse large B cell lymphoma (DLBCL), with rare cases developing into Hodgkin lymphoma (EBV Related)
- Rare cases of plasmablastic lymphoma (PBL) or B lymphoblastic leukemia / lymphoma have been reported
  - Cell cycle deregulation by TP53 and CDKNA2 mutations in over 50% of cases
  - NOTCH1 mutations and trisomy 12 in almost 33% of cases
- Immunophenotype: Increased intensity of CD38, ZAP70, HLA-DR, CD71
- Majority of DLBCL transformations from CLL / SLL retain the expression of CD5 and CD23 by flow cytometry

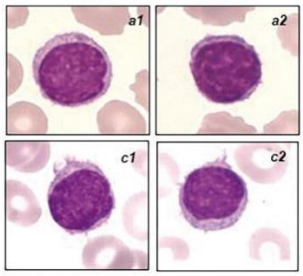
## Splenic B-cell neoplasms

### HAIRY CELL LEUKEMIA



- HCL involves the bone marrow, spleen, and peripheral blood. Significant lymphocytosis is infrequent. Lymphadenopathy and infiltration of extranodal sites is rare.
- Patients usually present with pancytopenia (**including monocytopenia**), low-level circulating leukaemic cells, and splenomegaly.
- characteristic immunophenotype of HCL is expression of bright surface immunoglobulin, CD20, CD22, CD11c, CD103, CD25, CD123, TBX21 (T-bet), ANXA1, FMC7, CD200, and cyclin D1.
- Desirable: clonal BRAF p.V600E (NP_004324.2) mutation

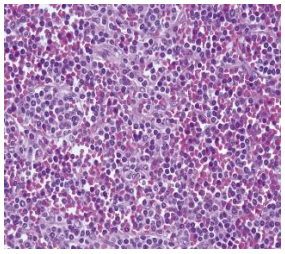
### SPLENIC MARGINAL ZONE LYMPHOMA

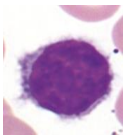



- Peripheral blood smears demonstrate a heterogeneous population of atypical mature small to intermediate-sized lymphocytes with variable amounts of pale-staining cytoplasm, with rare cells exhibiting polar villous extensions.
- positive expression of pan–B-cell markers, IgM, and IgD, and negative for BCL6, ANXA1, CD103, cyclin D1, SOX11, and LEF1; exclusion of other splenic and nodal B-cell lymphomas; clinical or imaging studies that show splenomegaly. Mutations in NOTCH2 and KLF2
- Desirable: neoplastic cells that are negative for CD5 and CD10.

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

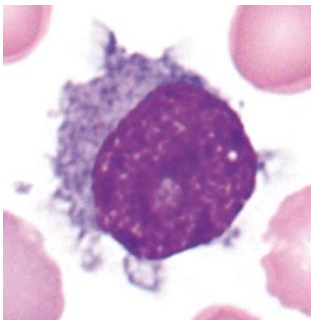
### SPLENIC DIFFUSE RED PULP SMALL B-CELL LYMPHOMA





- Splenic diffuse red pulp small B-cell lymphoma (SDRPL) is a small B-cell lymphoma involving the spleen, bone marrow, and peripheral blood, characterized by diffuse infiltration of the splenic red pulp by a monomorphic lymphoid population associated with circulating tumour cells bearing cytoplasmic projections.
- SDRPL is positive for B-cell markers (CD20, CD19, CD79a), DBA44, and IgG, but negative for CD5, CD23, CD43, cyclin D1, CD21, CD10, CD25, CD38, and ANXA1
- Essential: diffuse infiltration of the spleen by monomorphic small B cells, accompanied by atrophic white pulp; immunophenotype compatible with SDRPL.
- Desirable: absence of BRAF p.V600E

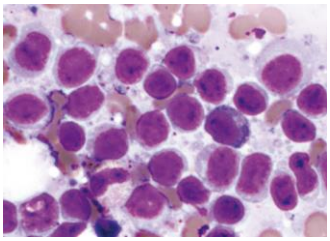
### SPLENIC B-CELL LYMPHOMA/LEUKAEMIA WITH PROMINENT NUCLEOLI

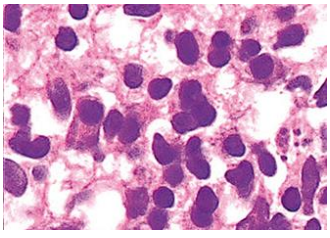


- Splenic B-cell lymphoma/leukaemia with prominent nucleoli (SBLPN) is a splenic B-cell neoplasm mimicking features of cells of hairy cell leukaemia (HCL); it lacks BRAF mutation and is resistant to conventional HCL therapy. Characteristically, the cells have a single large nucleolus.
- Immunophenotype: pan–B-cell antigens (CD19, CD20, and CD22), DBA44, CD11c, CD103, and FMC7, but not HCL markers (CD25, ANXA1, TRAP, and CD123)
- BRAF p.V600E mutation is absent, but MAP2K1 mutations are present probably in 38–42% of cases. Other genetic events include KMT2C mutations, U2AF1 and CCND3 mutations (~21–24%), and 7q deletions. TP53 mutations and/or 17p deletions and MYC alterations seem to be associated with a high risk.

## Lymphoplasmacytic lymphoma

### LYMPHOPLASMACYTIC LYMPHOMA



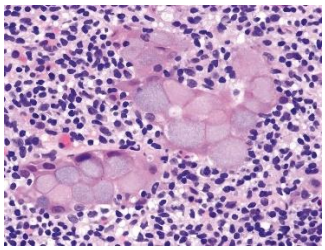


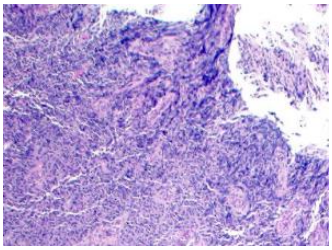
- IgM-type lymphoplasmacytic lymphoma / Waldenström macroglobulinaemia (IgM-type LPL/WM); non–IgM-type lymphoplasmacytic lymphoma / Waldenström macroglobulinaemia (non–IgM-type LPL/WM)
- The bone marrow is infiltrated by small B lymphocytes, plasmacytoid cells, and plasma cells. Plasmacytoid differentiation with Dutcher bodies is useful in the differential diagnosis with MZL as well as increase in reactive mast cells, haemosiderin-laden histiocytes.
- Most cases show a combined paratrabecular and interstitial infiltration pattern
- LPL cells express B-cell antigens such as CD20, CD19, CD22, CD79a, and PAX5. Other markers, such as CD45, CD25, and CD38, are usually positive.
- Essential: significant bone marrow infiltration by clonal small lymphocytes with plasmacytoid and/or plasma cell differentiation; immunophenotype of LPL cells: IgM+ (rarely IgG+ or IgA+), CD19+, CD20+, CD22+, CD25+, CD5−, CD10−, CD23−, CD103−, CD138+/−.
- Desirable: detection of MYD88 p.L265P; detection of CXCR4 somatic sequence variant; serum electrophoresis and immunofixation showing presence of monoclonal IgM (rarely IgG or IgA).

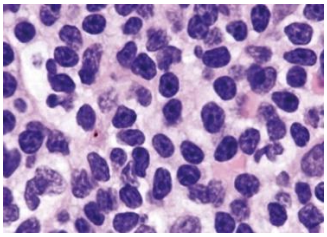
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

# Marginal Zone lymphoma

## EXTRANODAL MARGINAL ZONE LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE

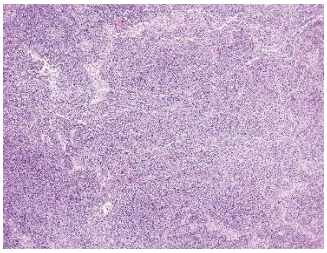


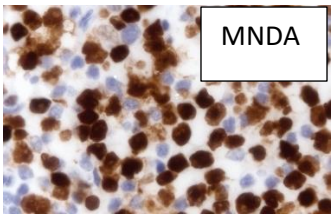




- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (EMZL) is an indolent primary extranodal B-cell lymphoma with cytological and architectural features reminiscent of Peyer patch lymphoid tissue, the prototypical mucosa-associated lymphoid tissue (MALT). EMZL typically arises from marginal zone B cells of acquired MALT and is often associated with an underlying chronic inflammatory disorder.
- t(11;18)(q21;q21): BIRC3 (API2)-MALT1 (6 - 26%)→ Gastric MALT
  - Associated with resistance to H. pylori eradication therapy
- t(14;18)(q32;q21): IGH-MALT1 (1 - 5%)
- t(X;14)(p11;q32)/IGH::GPR34 → Salivary gland MALT
- t(1;14)(p22:q32): BCL10-IGH (not seen in gastric cases)
- t(3;14)(p13;q32): FOXP1-IGH (not seen in gastric cases)
- Trisomy 3 (11%)
- Trisomy 18 (6%)
- Neoplastic cells express CD20, CD79a, MNDA and PAX5; usually IgM; IgG4 expression can be found in dural EMZL and primary cutaneous marginal zone lymphoma, without associated IgG4-related disease
- EMZL is typically negative for CD5, CD10, BCL6, CD23, cyclin D1, and SOX11
- Immunoprofile: CD19, CD79a, and negative for CD10 and CD5

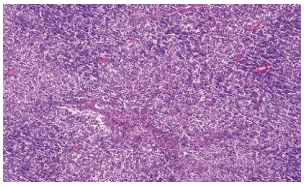
## NODAL MARGINAL ZONE LYMPHOMA






- Nodal marginal zone lymphoma (NMZL) is a primary nodal lymphoma of small, mature B cells derived from marginal zone B cells, without involvement of extranodal sites or the spleen.
- Lymph node shows diffuse effacement of the architecture by a monotonous small lymphoid infiltrate.
- The neoplastic cells are small lymphoid cells with minimally indented nuclei and moderate pale-staining cytoplasm.
- Immunohistochemistry for CD20 shows sheets of small B cells effacing the lymph node architecture and for MNDA shows diffuse nuclear expression in the lymphoma cells.
- **PTPRD mutations are more common in NMZL**
- Most NMZLs express pan–B-cell markers (CD19, CD20, CD79a, or PAX5) and BCL2, MNDA, IRTA1 and a variable proportion express CD43

## PAEDIATRIC NODAL MARGINAL ZONE LYMPHOMA

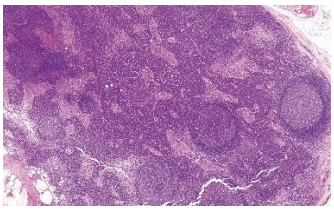


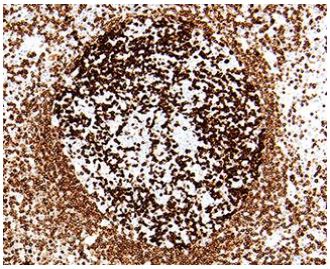
- Paediatric nodal marginal zone lymphoma (PNMZL) is a primary nodal mature B-cell neoplasm, mostly occurring in the head and neck region of adolescent boys. PNMZL shares the interfollicular expansion of clonal marginal zone B cells. Nevertheless, the specific clinical and histomorphological features differ from those of the adult counterpart.
- peripheral lymphadenopathy, localized stage I/II disease→ good prognosis
- Positive: CD20, CD19, CD79a, CD43, MUM1, BCL2, light chain restriction
- CD23 is negative but may identify disrupted follicular dendritic cell

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

# Follicular lymphoma

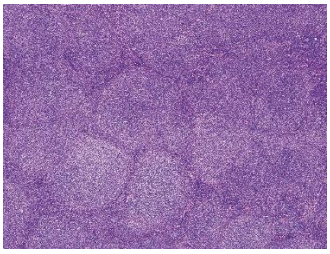
## IN SITU FOLLICULAR B-CELL NEOPLASM

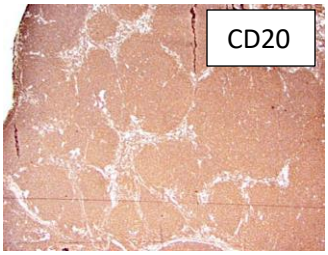


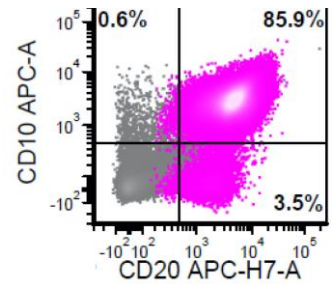


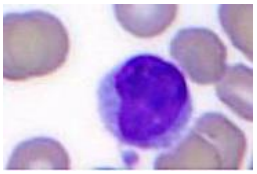
- In situ follicular B-cell neoplasm (ISFN) is defined as partial or complete colonization of some reactive germinal centres by follicular B cells with IGH::BCL2 fusion and strong BCL2 expression in otherwise normal reactive lymph node.
- ISFN may be detected concurrently with or subsequent to follicular lymphoma (FL)
- Like FL, ISFN demonstrates t(14;18)(q32;q21)/IGH::BCL2 and shows imprints of activation-induced cytidine deaminase (AID)-mediated genomic instability.
- ISFN can be readily identified by immunostaining for BCL2 and CD10.
  - The ISFN cells are strongly positive for BCL2 and CD10 in contrast to the surrounding mantle zone B and T cells

## FOLLICULAR LYMPHOMA





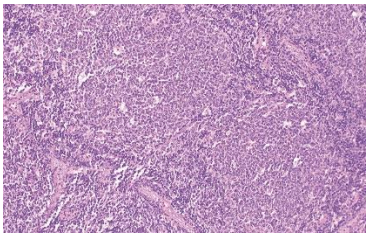



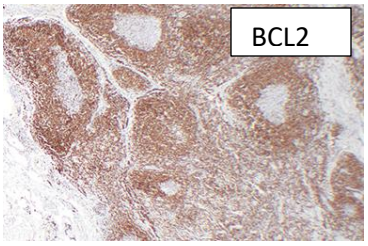



- Follicular lymphoma (FL) is a neoplasm of germinal-centre (GC) B cells with varying proportions of centrocytes and centroblasts or large transformed cells and at least a partially follicular growth pattern.
  - FL with BCL2 rearrangement
  - FL with BCL6 rearrangement
  - FL with BCL2 and BCL6 rearrangement
  - FL with unusual cytological features
  - FL with a predominantly diffuse growth pattern
  - Follicular large B-cell lymphoma
- Bone marrow events:
  - t(14;18) (q32;q21) translocation: repair failure during V(D) J recombination
  - t(14;18) (q32;q21) IGH / BCL2: 85% of follicular lymphomas
  - BCL2 expression in precursor follicular lymphoma cells: increase survival in germinal center
- Germinal center events
  - Retain germinal center functionality (e.g. BCL6)
- Molecular changes
  - Chromatin modification (KMT2D, EZH2, CREBBP, ARID1A, MEF2B, EP300)
  - B cell receptor signaling (CARD11, IgHV, IgLV)
  - Cell cycle regulation (RB1, CDK4)
  - Transcription factor (FOXO1, MEF2B)
  - Immune evasion (EPHA7, TNFRSF14, CREBBP)
- Flow: CD20 bright+, CD19 dim+, CD10+, CD5-, cyclin D1-
- Positive stains: Monotypic surface Ig, CD19, CD20, CD22, CD79a, CD10, BCL6, HGAL, LMO2 (CD10 and BCL6 are weaker in interfollicular cells), BCL2, CD21, CD23, or CD35 (Dendritic cell meshwork)
- Negative stains: CD5 (can be focally positive), CD43, CyclinD1

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

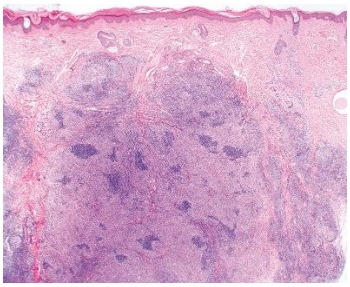
## PAEDIATRIC-TYPE FOLLICULAR LYMPHOMA

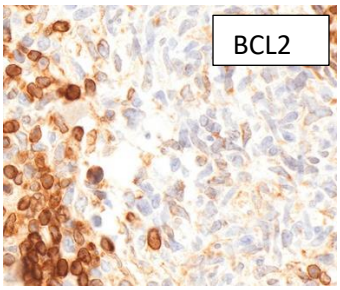





- Pediatric-type follicular lymphoma (PTFL) is a localized, nodal mature B-cell lymphoma occurring predominantly in the pediatric, adolescent, and young adult age group.
- It is characterized by a clonal proliferation of germinal-center B cells with a pure follicular growth pattern, altered lymph nodal architecture, a high proliferation index, **and an absence of BCL2, BCL6, MYC and IRF4 rearrangements.**
- Recurrent alterations in PTFL include deletions and copy-neutral loss of heterozygosity at 1p36 **and mutations of TNFRSF14 (44–54%) and MAP2K1 (43–49%)**
- The neoplastic cells coexpress B-cell markers ( CD20, CD79a, and PAX5) and germinal-center markers (strong BCL6 and CD10)
- There is very faint expression of BCL2 in the areas of atypical follicles

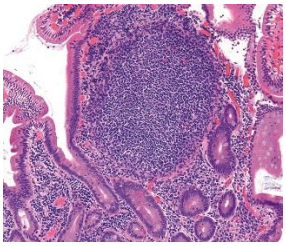
## PRIMARY CUTANEOUS FOLLICLE CENTER LYMPHOMA

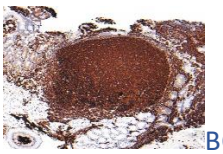





- Primary cutaneous follicle center lymphoma (PCFCL) is a tumor of follicle center cells, including centrocytes and variable numbers of centroblasts, with a follicular or diffuse growth pattern, that generally occurs in the skin of the head or trunk.
- PCFCL is a monoclonal proliferation of germinal centre–derived B cells, which harbour clonally rearranged IG genes, with somatic hypermutation
- Essential: follicular and/or diffuse proliferation of centrocytes and admixed centroblasts
- B cells with coexpression of germinal-centre markers (BCL6 and/or CD10 or other germinal-center markers); no extracutaneous involvement by lymphoma.
- Desirable: localization to head or trunk; evidence of B-cell monoclonality; **absent or weak BCL2 expression** (usually); lack of IRF4 (MUM1) expression; lack of BCL2 rearrangement (usually).

## DUODENAL-TYPE FOLLICULAR LYMPHOMA



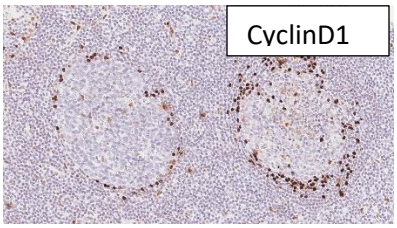

BCL2

- Duodenal-type follicular lymphoma (DTFL) is a variant of follicular lymphoma (FL) restricted to the gastrointestinal tract, mainly to the second portion of the duodenum.
- In most cases, there are additional lesions throughout the small intestine and, less commonly, in the stomach, colon, and rectum
- The pathogenesis of DTFL shows many similarities with the early steps of nodal/systemic FL pathogenesis, in **that t(14;18)(q32;q21) (IGH::BCL2) and recurrent mutations in TNFRSF14, EZH2, KMT2D, and/or CREBBP** are found in almost all cases.
- The tumour cells show a phenotype similar to that of nodal/systemic FL, being positive **for CD10, BCL6, and BCL2,** B-cell antigens. Follicular dendritic cell meshworks (CD21/CD23/CD35+) are pushed to the periphery of the neoplastic follicles, in contrast to the preserved meshworks usually seen in nodal/systemic FL. The prognosis is excellent.

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## Mantle cell lymphoma

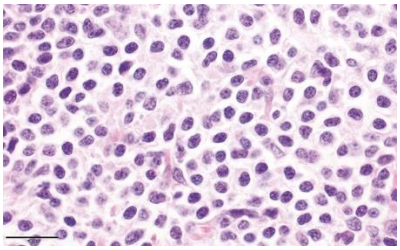
### IN SITU MANTLE CELL NEOPLASM

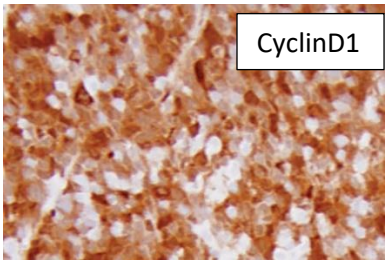



cells are restricted to the inner layer of the mantle zone

- In situ mantle cell neoplasm (ISMCN) is defined by the presence of cyclin D1–positive B cells, usually with CCND1 rearrangement, restricted to usually non-expanded mantle zones of lymphoid follicles.
- ISMCN is most often found in lymph nodes but may be seen in extranodal lymphoid tissues. Involvement of more than one site does not exclude the diagnosis
- IHC: Pan B-cell markers, CyclinD1, IgD, and BCL2; Variable Sox11
- Negative stains: CD5 and CD43 (more often negative than MCL)

### MANTLE CELL LYMPHOMA

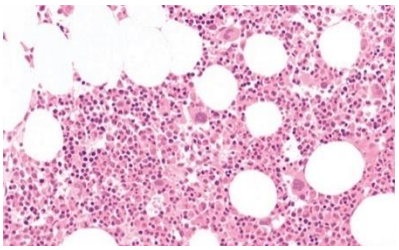





- Mantle cell lymphoma (MCL) is a mature B-cell neoplasm derived from the mantle zone of lymphoid follicles and typically composed of small to medium-sized monomorphic cells expressing CD5, SOX11, and cyclin D1. It is associated with CCND-family rearrangements, most commonly CCND1.
- **Cyclin D1–positive MCL**
- Essential: lymphoma cells of B lineage (positive for CD20 and usually CD5); cyclin D1 positivity and/or detection of CCND1 rearrangement.
- Desirable: SOX11 expression positivity.

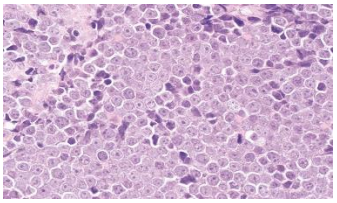
- **Cyclin D1–negative MCL**
- Essential: lymphoma cells of B lineage (positive for CD20 and usually CD5); immunophenotype consistent with MCL, including SOX11 expression; **absence of cyclin D1 expression and CCND1 rearrangement.**
- Desirable: CCND2 rearrangement.

### LEUKAEMIC NON-NODAL MANTLE CELL LYMPHOMA



- Leukemic non-nodal mantle cell lymphoma (nnMCL) is characterized by the involvement of blood, bone marrow, and spleen by neoplastic cells with morphological and immunophenotypic similarities to nodal mantle cell lymphoma (MCL), with absent or minimal evidence of lymphadenopathy, and usually with an asymptomatic presentation.
- Immunophenotype: CD20, CyclinD1, and CD5 (most cases); SOX11 is lower or negative.
- Molecular: Detection of CCND1 rearrangement by FISH

### TRANSFORMATIONS OF INDOLENT B-CELL LYMPHOMAS



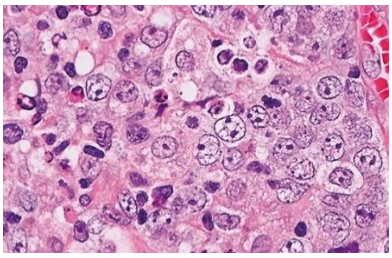
- Transformation is defined as the emergence of an aggressive lymphoma type in a patient with a previously or synchronously diagnosed clonally related indolent B-cell lymphoma. Transformed lymphomas should be reported according to their aggressive lymphoma entity, followed by adding the term “transformed from” and the denominator of the indolent lymphoma from which they have evolved.
- Often, the transformed blasts retain immunophenotypic features of their low-grade counterparts, **such as CD10 and BCL6 expression** in cases transformed **from follicular lymphoma**, or **CD5 or CD23 expression in RT**

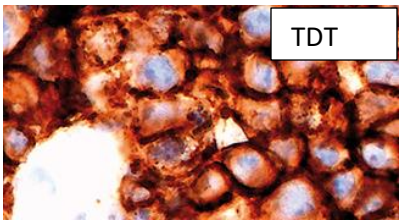
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

***Large B-cell lymphomas***

- Diffuse large B-cell lymphoma, NOS
- Diffuse large B-cell lymphoma, centroblastic subtype
- Diffuse large B-cell lymphoma, immunoblastic subtype
- Diffuse large B-cell lymphoma, anaplastic subtype
- Diffuse large B-cell lymphoma, germinal-centre B-cell subtype
- Diffuse large B-cell lymphoma, activated B-cell subtype
- Diffuse large B-cell lymphoma with MYC and BCL6 rearrangements

## DIFFUSE LARGE B-CELL LYMPHOMA NOS

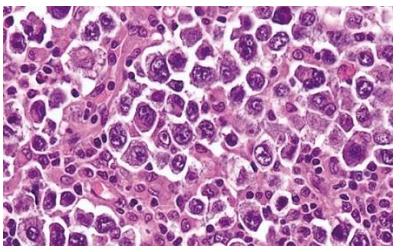





TDT can be positive in a subset of cases of DLBCL NOS, and does not justify diagnosis of B-ALL, if other markers including CD20, MYC, BCL2, BCL6, and or IRF4 are positive

- Diffuse large B-cell lymphoma (DLBCL) NOS is a lymphoma consisting of medium-sized to large B cells with a diffuse growth pattern. This entity does not meet the diagnostic criteria for any specific large B-cell lymphoma neoplasms.
- Lymphoma cells express CD45 and pan–B-cell markers (CD19, CD20, CD22, CD79a, and PAX5) and expression of GC markers (CD10, BCL6, LMAO2 in GCB type; or non-GCB type/activated B-cell (IRF4/MUM1) ; Rare cases may show aberrant CD3 expression, confounding lineage assignment. CD5 expression is assocaited with worse outcome.
- The majority of DLBCL-NOS cases express BCL2, and the intensity of expression is variable. Similarly, expression of MYC protein is highly variable. In most studies, BCL2 is considered positive if ≥ 50% of the tumour cells are positive, and MYC is considered positive if ≥ 40% of the tumour cell nuclei are positive.
- *Essential:* a large B-cell lymphoma with a diffuse or vaguely nodular growth pattern; mature B-cell phenotype; exclusion of other specific entities of large B-cell lymphoma.
- *Desirable:* cell of origin (COO) subtyping (GCB vs non-GCB subtypes; HANS algorithm); reporting of isolated *MYC* or dual *MYC* and *BCL6* rearrangements; genetic testing
- Molecular: TP53 mutation in combination with MYC →poor outcome

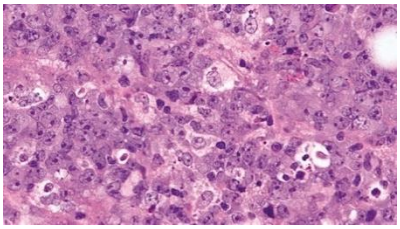
## DIFFUSE LARGE B-CELL LYMPHOMA, ANAPLASTIC VARIANT



- This subtype is rare and accounts for about 3% of all DLBCL cases.
- It is characterized by large to very large lymphoma cells, with pleomorphic or bizarre nuclei, usually abundant cytoplasm, and frequent cohesive sheet-like growth, and partial or extensive sinusoidal involvement. This variant often expresses CD30 and has frequent TP53 mutations→ poor outcomes
- These pathological features may mimic those of classic Hodgkin lymphoma with syncytial growth, anaplastic large cell lymphoma, ALK-positive large B-cell lymphoma, or undifferentiated carcinoma.

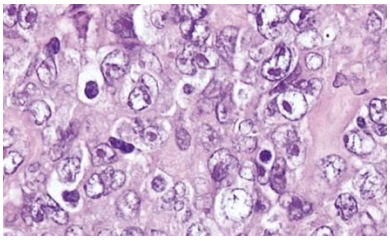
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## DIFFUSE LARGE B-CELL LYMPHOMA, CENTROBLASTIC SUBTYPE



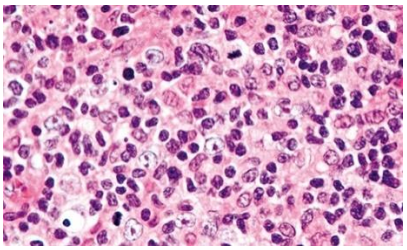
- The centroblastic subtype is the most common, accounting for approximately 80% of cases. Centroblasts are large lymphocytes with variable amounts of cytoplasm, round to oval nuclei, fine to vesicular chromatin, and several small to medium nucleoli often adjacent to the nuclear membrane.
- Monomorphic cases are composed predominantly (> 90%) of centroblasts, whereas polymorphic tumours consist of a mixture of centroblasts (< 90%), large centrocytes, and immunoblasts
- Cases with many large lymphocytes with multilobated nuclei and clear cytoplasm can be observed, particularly at extranodal sites.
- Features of plasmacytic differentiation can be rarely seen.

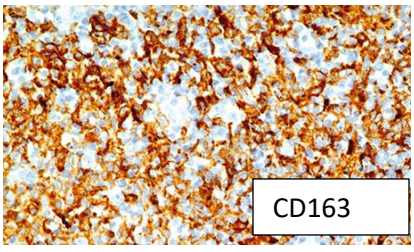
## DIFFUSE LARGE B-CELL LYMPHOMA, IMMUNOBLASTIC SUBTYPE



- This subtype is less common, representing 8–10% of all cases, and is traditionally defined by presence of ≥ 90% immunoblasts in the cell composition of the lymphoma.
- Immunoblasts are large lymphocytes with moderate to abundant basophilic cytoplasm and a single prominent, centrally located nucleolus.
- Cytological variability occurs, which may account for the variable intraobserver and interobserver reproducibility in the diagnosis of this variant.
- In some cases, the immunoblasts show plasmacytic differentiation. This variant has been associated with an inferior prognosis compared with other DLBCL variants and is characterized by frequent IGH::MYC translocations

## T-CELL/HISTIOCYTE-RICH LARGE B-CELL LYMPHOMA

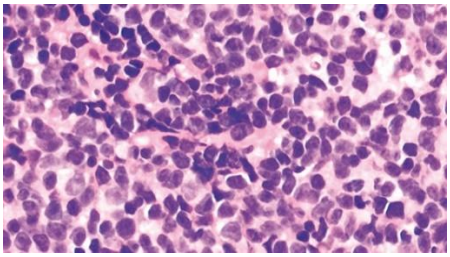


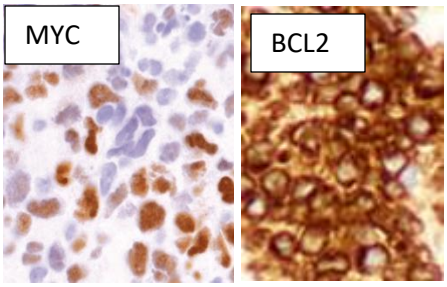



- T-cell/histiocyte–rich large B-cell lymphoma (THRLBCL) is an aggressive B-cell lymphoma with < 10% large neoplastic B cells, scattered in a diffuse background rich in T cells and histiocytes, and with a virtual absence of small B cells.
- A subset of cases show marked clinical, immunophenotypic, and molecular overlap with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL, commonly known as nodular LP).
- Immunophenotype: Pan B-cell markers, CD45, MEF2B, and BCL6; IRF4 and EMA are variable. CD30, CD10, and EBV are absent.
- Molecular: The neoplastic B cells show monoclonally rearranged IG genes, although these may not be demonstrable in cases with low numbers of neoplastic B cells. Tcell receptor genes are germline.

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

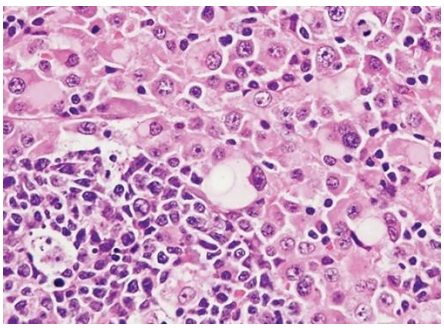
## DIFFUSE LARGE B-CELL LYMPHOMA / HIGH-GRADE B-CELL LYMPHOMA WITH MYC AND BCL2 REARRANGEMENTS





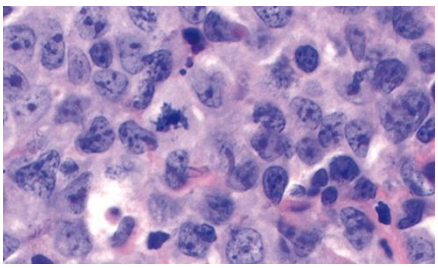

- Diffuse large B-cell lymphoma / high-grade B-cell lymphoma with MYC and BCL2 rearrangements (DLBCL/HGBCL-MYC/BCL2) is an aggressive mature B-cell lymphoma with structural chromosomal aberrations with breakpoints at both MYC and BCL2 loci.
- Although the lymph nodes are most commonly involved, a high proportion (30–88%) of cases show additional involvement of more than one extranodal site such as the bone marrow or CNS.
- IHC: pan–B-cell antigens with IRF4 (MUM1), BCL2, and MYC (Variable intensity) as well as CD10 and BCL6 in vast majority.
- Consequently, 91–99% of these tumours have a germinal-centre B-cell (GCB)-like phenotype
- Essential: morphology and phenotype consistent with an aggressive B-cell lymphoma; evidence of concurrent MYC and BCL2 rearrangements (with or without BCL6 rearrangement).

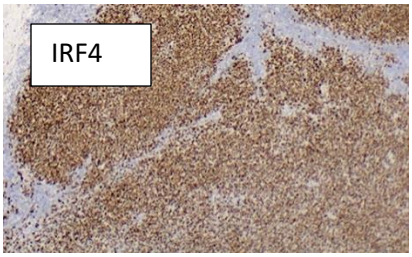
## ALK-POSITIVE LARGE B-CELL LYMPHOMA



- Anaplastic lymphoma kinase–positive large B-cell lymphoma (ALK+ LBCL) is a diffuse, monomorphic neoplasm of large B cells with a plasmablastic immunophenotype and ALK expression due to ALK rearrangement.
- IHC: ALK (Cytoplasmic and granular pattern most common), CD138, IRF4, VS38S, and variable CD20. Also positive EMA, BOB1, OCT2, MYC
- Negative Stains: CD19, CD22, CyclinD1, BCL2
- Molecular: Translocations, inversions, and insertions involving ALK at chromosome 2p23 play an essential role in pathogenesis.

## LARGE B-CELL LYMPHOMA WITH IRF4 REARRANGEMENT

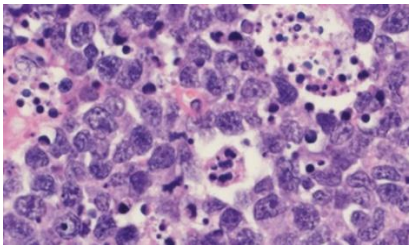


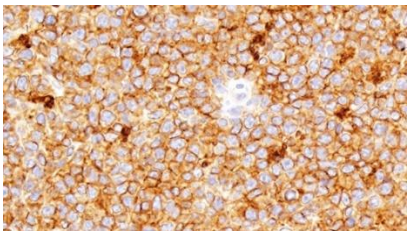



- Large B-cell lymphoma (LBCL) with IRF4 rearrangement is a de novo mature B-cell lymphoma with a follicular and/or diffuse growth pattern, defined by strong expression of IRF4 (MUM1), usually due to an IG::IRF4 translocation.
- LBCL-IRF4 typically involves the Waldeyer ring or cervical lymph nodes, less commonly Peyer patches. Most common in children
- IHC: Mature B-cell phenotype, **strong IRF4 (MUM1) and BCL6**
- CD10 and BCL2 are expressed in 50% of cases, and CD5 is observed in about 30%.
- *Essential:* intermediate or large cell morphology and a follicular and/or diffuse growth pattern; mature B-cell phenotype with coexpression of BCL6 and IRF4 (MUM1); *IRF4* translocation; if *IRF4* rearrangement analysis cannot be performed, the proper clinical setting in combination with a typical immunophenotype allows the diagnosis, but as “not molecularly confirmed”.
- *Desirable:* evidence of the IG::*IRF4* translocation; absence of *BCL2* and *MYC* gene rearrangement.

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

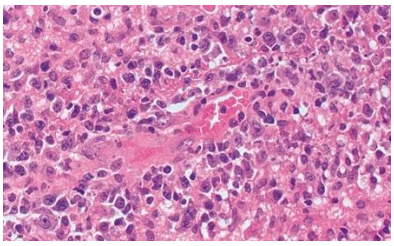
## HIGH-GRADE B-CELL LYMPHOMA WITH 11Q ABERRATION





- High-grade B-cell lymphoma with 11q aberration (HGBCL-11q) is an aggressive mature B-cell lymphoma with a morphology similar to that of Burkitt lymphoma or showing an intermediate to blastoid appearance in most cases and a characteristic chromosome 11q-gain/loss pattern.
- Cases with concomitant MYC rearrangements are excluded.
- The presence of the 11q gain is less specific for HGBCL-11q than the telomeric loss / LOH of 11q
- *Essential:* lymphoma with an intermediate/blastoid or Burkitt-like morphology; typical immunophenotype (B-cell markers+, CD10+, BCL6+, BCL2−); chromosome 11q gain/loss, telomeric loss, or telomeric LOH pattern; exclusion of a *MYC* translocation.
- *Desirable:* expression of CD56 in the absence of CD38 by flow or IHC

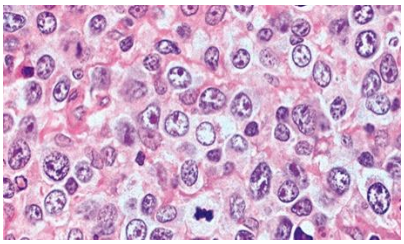
## LYMPHOMATOID GRANULOMATOSIS

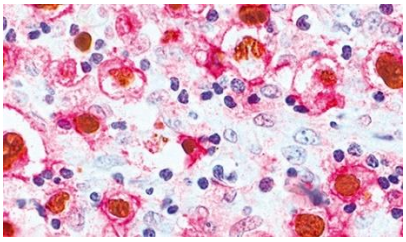


polymorphic angiocentric infiltrates

- Lymphomatoid granulomatosis (LYG) is an EBV-associated angiocentric and angiodestructive B-cell lymphoproliferative disorder involving extranodal sites, **composed of EBV-positive atypical large B cells**, in patients with acquired immunodeficiency/dysregulation
- Lymphomatoid granulomatosis, grade 1; lymphomatoid granulomatosis, grade 2; lymphomatoid granulomatosis, grade 3
- IHC: CD20, CD30, EBER; background T-cells: CD3, CD4, and CD8
- Molecular: grade II and III LYG show clonality for IG genes

## EBV-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA

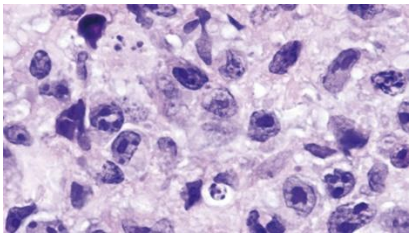


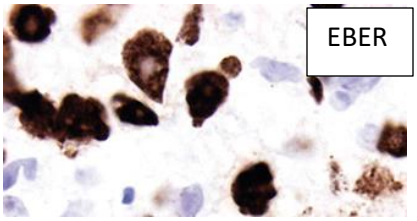


- Epstein Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL) is a large B-cell lymphoma in which the majority of the neoplastic cells harbour EBV.
- Older patients with a male predominance
- Affected patients do not have a history of lymphoma or underlying immune deficiency/dysregulation. The neoplasm should not fulfil criteria for other EBV+ lymphoproliferative disorders or lymphomas.
- Cases in younger patients (aged < 45 years) often show predominantly nodal involvement, which can be localized or generalized
- IHC: PanB cell antigent, EBER ISH, CD30 (variable), MUM1, BCL6 (variable), PDL1; Negative for CD10, CD15
- Molecular: Monoclonal IgH rearrangements; EBV RNA/DNA

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

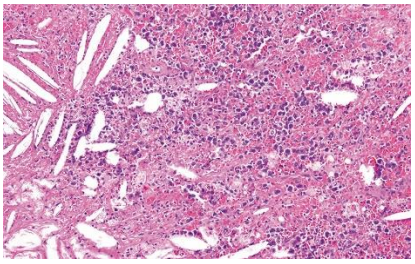
## DIFFUSE LARGE B-CELL LYMPHOMA ASSOCIATED WITH CHRONIC INFLAMMATION





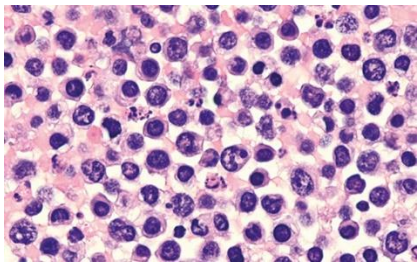

- Diffuse large B-cell lymphoma (DLBCL) associated with chronic inflammation (CI-DLBCL) is an EBV-associated neoplasm occurring in the setting of longstanding chronic inflammation involving confined body spaces.
- Pyothorax-associated lymphoma (PAL) is the prototypical form, developing in the pleural cavity of patients with longstanding pyothorax.
- IHC: B-cell markers often with activated B-cell phenotype, with plasmablastic differentiation (CD138, MUM1); CD30 maybe expressed; **aberrant expression of 1 or 2 T-cell markers** (CD2, CD3, CD4, CD7); EBV/EBER is characteristic.

## FIBRIN-ASSOCIATED LARGE B-CELL LYMPHOMA



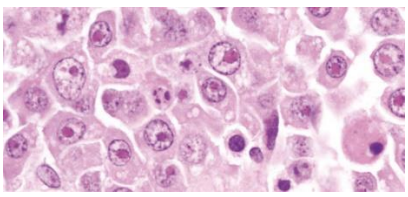
- Fibrin-associated large B-cell lymphoma (FA-LBCL) is a neoplasm of large B cells found incidentally at sites of chronic fibrin deposition in confined body sites, without infiltration into normal parenchyma.
- Is associated with EBV infection, but rare EBV-negative cases have also been described
- IHC: Pan-B cell markers with an activated B-cell immunophenotype, MUM1, Variable (CD30, BCL2, and BCL6), aberrant T-cell expression, a high Ki-67, and EBER is almost always positive

## FLUID OVERLOAD-ASSOCIATED LARGE B-CELL LYMPHOMA



- Fluid overload–associated large B-cell lymphoma is a B-cell neoplasm presenting as serous effusions without detectable tumor masses, often in patients with fluid overload states and not associated with KSHV/HHV8; but maybe associated with HCV, HBV, or EBV
- IHC: PanB-cell markers (however reduced CD20 expression), variable (CD138 , CD10, and CD30).
- Molecular: clonal IG gene rearrangement.

## PLASMABLASTIC LYMPHOMA

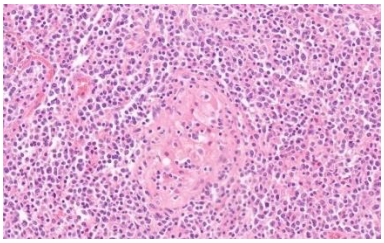


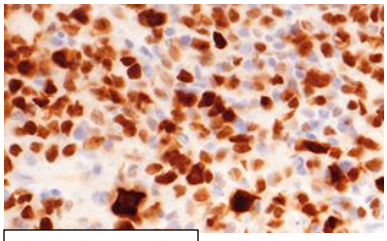
BLIMP1. nuclear

- Plasmablastic lymphoma (PBL) is an aggressive Terminal B-cell neoplasm composed of large atypical B cells with plasmablastic or immunoblastic morphology and is associated with HIV/EBV/ and immunodeficiency. Also associated with CART-therapy
- Predominantly at extranodal sites (Head and Neck)
- Positive stains: CD138, CD38, VS38c, BLIMP1 and XBP1 in most
- Negative stains: CD20, PAX-5, CD79a (Variable), CD45
- Molecular: Monoclonal IG rearrangements can be seen
- Essential: lymphoma with plasmablastic/immunoblastic morphology; expression of plasma cell–associated markers (e.g. IRF4 [MUM1], CD138, Blimp1); negativity for CD20, PAX5, ALK, and KSHV/HHV8.

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## PRIMARY LARGE B-CELL LYMPHOMA OF IMMUNE-PRIVILEGED SITES

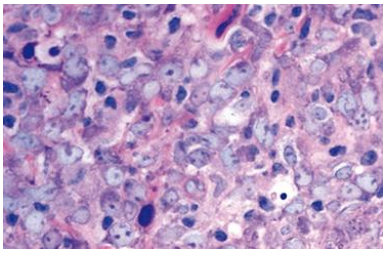




BCL-6

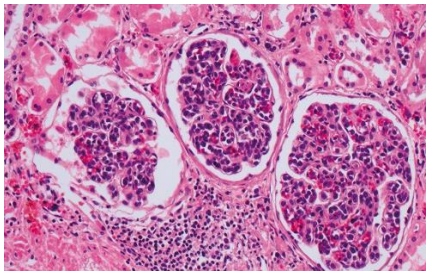
- Primary large B-cell lymphomas (LBCLs) of immune-privileged sites (IP-LBCLs) comprise LBCLs that arise as primary tumors in the CNS, vitreoretinal, and testis of immunocompetent patients.
- Excluded from this category are the lymphomas that arise in the dura and the choroid, lymphomas that secondarily involving these sites, and lymphomas occurring in immune deficiency/dysregulation
- Single or multiple grey to yellow masses are seen within the parenchyma, with varying degrees of demarcation→ avoid steroid prior to BX
- Positive stains: PanB-cell markers (post-germinal) , IRF4, BCL2, BCL6, and IgM, high Ki-67
- Negative stains: EBV (positivity should raise ddx for another lymphoma)
- Molecular: demonstration of a clonal B-cell population or MYD88 and/or CD79B hotspot mutations in cases in which histology is not definitive

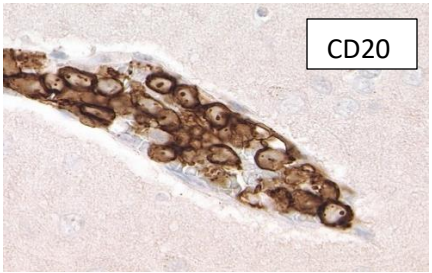
## PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE



- Primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL-LT), is a lymphoma composed exclusively of centroblasts and immunoblasts, most commonly arising in the leg.
- Histology: Pandermal dense diffuse infiltration by large cells, sparing the epidermis
- IHC: PanB-cell markers, Strong BCL2 by IHC( Lack BCL2 rearrangement), Strong IRF4, FOXP1, MYC. Variable BCL6 and almost negative CD10
- Molecular: presence of *MYD88* and/or *CD79B* mutations favours PCLBCL-LT.

## INTRAVASCULAR LARGE B-CELL LYMPHOMA



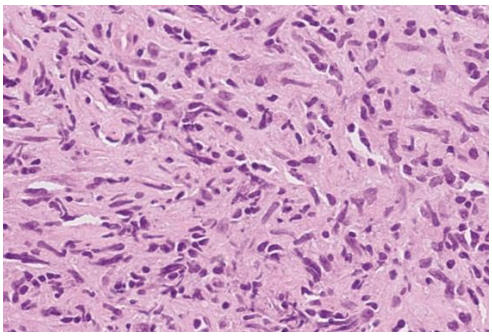


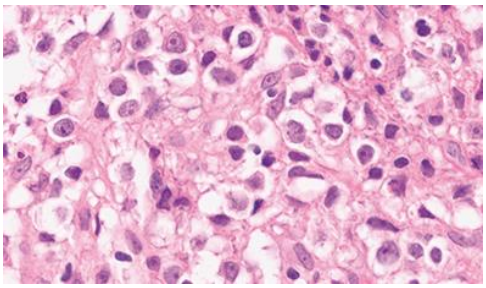
CD20

- Intravascular large B-cell lymphoma (IVLBCL) is an aggressive extranodal B-cell lymphoma characterized by the proliferation of large neoplastic B cells virtually exclusively within the lumina of blood vessels.
  - Classic subtype
  - Cutaneous subtype
  - Hemophagocytic subtype
- Histology: IVLBCL involving the kidney shows large, dark-staining lymphoid cells in glomerular capillaries and in a peritubular capillary.
- IHC: PanB-cell markers of non-germinal center type with IRF4 expression, coexpression of CD5 and PDL1; EBV and HHV8 negative

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

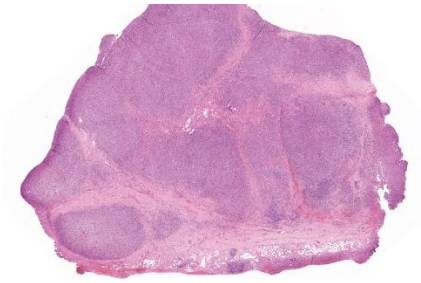
## PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

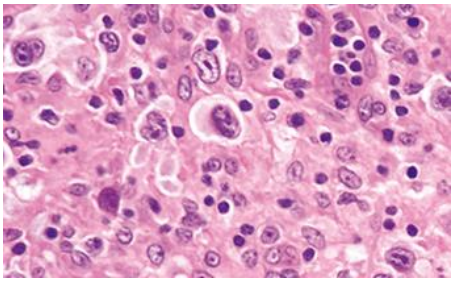


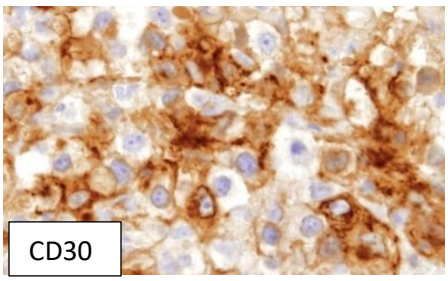


- Primary mediastinal large B-cell lymphoma (PMBCL) is a mature aggressive B-cell lymphoma of putative thymic B-cell origin, arising in the anterior mediastinum with distinctive clinical, immunophenotypic, and molecular features.
- Histology: There is wide morphological and cytological variation from case to case. Diffuse infiltration of large clear cells with abundant cytoplasm and alveolar compartmentalizing by fine fibrosis is typically common
- Positive stains: CD45, B-cell markers, CD30, IRF4, **CD23, MAL, CD200, PDL1 and PDL2 (Specific)**
- Negative stains: Surface and cytoplasmic IgG, BOB1, OCT2, PAX5, CD10, Variable BCL2 and BCL6
- Molecular: copy gain or rearrangement of the *CD274*/*PDCD1LG2* locus and/or rearrangement involving *CIITA* (*C2TA*).

## MEDIASTINAL GREY ZONE LYMPHOMA



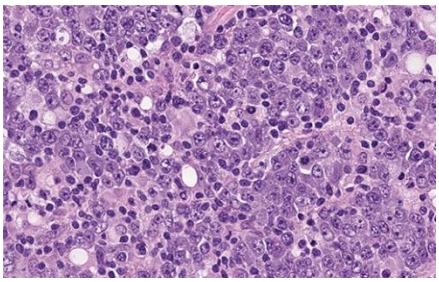


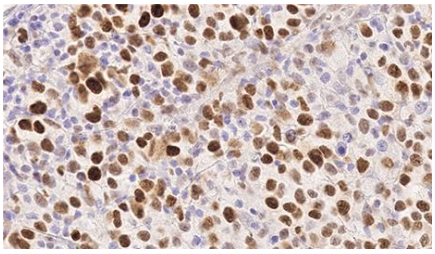



- Mediastinal grey zone lymphoma (MGZL) is a B-cell lymphoma with overlapping clinical, morphological, immunophenotypic, and molecular features between primary mediastinal B-cell lymphoma (PMBCL) and classic Hodgkin lymphoma (CHL), particularly nodular sclerosis CHL (NSCHL).
- Histology: nodular proliferation with fibrous septa, Higher magnification shows sheet-like growth of pleomorphic cells often resembling lacunar cells, with an inflammatory background
- IHC: The CHL cells show panB cell markers (CD20, CD19, CD79a, PAX5), CD30 (variable); CD15 (usually negative); if only CD20 and PAX5 are positive CHL is more favored. **EBV is usually negative.**
- A typical PMBCL morphology with preservation of B-cell markers but with an intense and diffuse expression of CD30, without CD15 expression, is not consistent with MGZL, and a diagnosis of PMBCL is preferred.
- Essential for CHL-like MGZL: confluent growth of pleomorphic cells within a variably abundant microenvironment and dense fibrotic stroma; uniform strong expression of CD20, PAX5, and at least one additional B-cell marker (CD19, CD79a, BOB1, OCT2); positive expression of CD30, with varying intensity.
- Essential for PMBCL-like MGZL: monomorphic sheets of medium-sized to large neoplastic cells within a variably dense fibrotic stroma; strong and uniform positive expression of CD30 and partial or complete loss of B-cell markers, or strong CD15 expression.
- Molecular: Lack BCL2 and BCL6 rearrangement; CIITA translocation. Negative for EBV in situ hybridization.

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## HIGH-GRADE B-CELL LYMPHOMA NOS

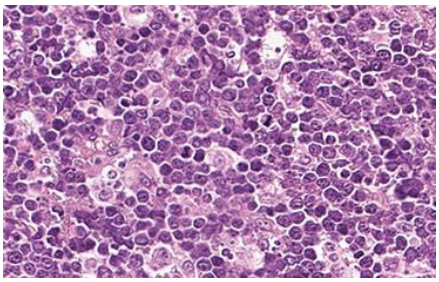


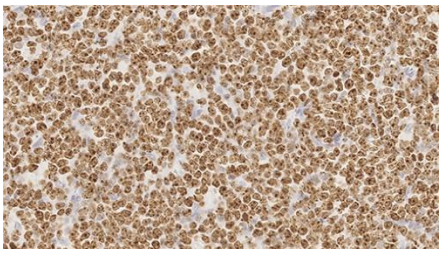


Variable MYC expression

- High-grade B-cell lymphoma (HGBCL) NOS represents a heterogeneous type of aggressive mature B-cell lymphoma composed of medium-sized or blastoid cells that does not fulfil the diagnostic criteria for other defined lymphoma entities.
- Morphology intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, characterized by a diffuse proliferation of medium-sized to large cells with a few admixed small lymphocytes. The cellular morphology is variable, exhibiting more variation in nuclear size and nucleolar content than generally acceptable for Burkitt lymphoma
- IHC: Pan-B cell markers and lack expression of CD34 and TDT, CD10, BCL6 and BCL2; IRF4 expression is variable. Ki-67 is variable
- *Essential:* intermediate or blastoid cytomorphology not consistent with either diffuse large B-cell lymphoma or Burkitt lymphoma; **absence of a dual translocation involving *MYC* and *BCL2***; absence of the 11q23.2-q23.3 gain and 11q24.1-qter deletion pattern of HGBCL with 11q aberration.
- *Desirable:* double-hit/dark-zone B-cell lymphoma gene expression signature; *KMT2D* and *TP53* mutations.

## BURKITT LYMPHOMA





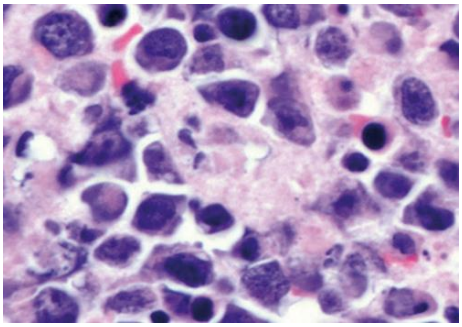
Strong MYC expression

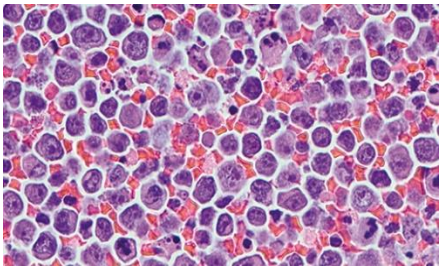
- Burkitt lymphoma (BL) is a mature aggressive B-cell neoplasm composed of monomorphic, medium-sized cells with basophilic cytoplasm, multiple small nucleoli, a germinal-center B-cell phenotype, a high proliferation index, and an IG::MYC rearrangement.
- BL occurring in HIV-positive individuals tends to present in patients with relatively high CD4 counts
- Diffuse growth pattern composed of monomorphic medium-sized lymphoid cells with basophilic cytoplasm, squared-off cytoplasmic borders, round nuclei with finely clumped and dispersed chromatin, and multiple basophilic and paracentrally located nucleoli. The cells display some degree of cohesion, with abundant mitoses and apoptosis. There is a starry-sky pattern due to the presence of many macrophages with phagocytic activity containing apoptotic debris
- IHC: Pan-B cell markers with a germinal center phenotype (CD10, BCL6, HGAL, MEF2B, GCET1), IgM, nuclear MYC, and high KI
- Negative: CD5, **BCL2,** TDT, CyclinD1, CD138, CD23, CD45 ( can be dim)
- Molecular: an IG::MYC rearrangement.

**KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas**

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

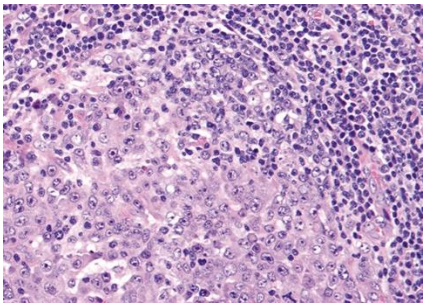
### PRIMARY EFFUSION LYMPHOMA





- Primary effusion lymphoma (PEL) is a large B-cell lymphoma presenting as a pleural, pericardial, and/or peritoneal serous effusion in the absence of lymph node involvement or an extranodal mass lesion.
- It is consistently associated with **Kaposi sarcoma–associated herpesvirus / human herpesvirus 8 (KSHV/HHV8)** and usually coinfected with EBV. Extracavitary PEL (EC-PEL) is a related entity presenting with a tumour mass, often at extranodal sites.
- Immunophenotype: Dim CD45, CD38, CD138, Vs138 and HLA-DR.
- The cells are negative for CD19, CD20, and surface/cyto light chain
- Essential for PEL: large B-cell lymphoma presenting as a serous effusion in the pleural, pericardial, or abdominal cavity; absence of lymph node or other extranodal involvement;
- Essential for EC-PEL*:* large B-cell lymphoma presenting with nodal or extranodal involvement without an associated effusion; large pleomorphic malignant cells with the immunophenotype of terminally differentiated B cells;
- *Desirable for both:* KSHV/HHV8 positivity (usually by LANA immunohistochemistry). presence of EBV is supportive.

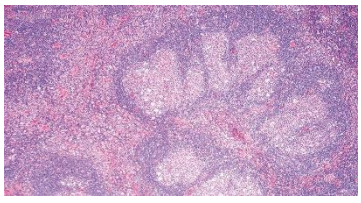
### KSHV/HHV8-POSITIVE GERMINOTROPIC LYMPHOPROLIFERATIVE DISORDER



- Kaposi sarcoma–associated herpesvirus / human herpesvirus 8 (KSHV/HHV8)-positive germinotropic lymphoproliferative disorder (KSHV/HHV8-positive GLPD) is characterized by KSHV/HHV8-positive and usually EBV-positive large atypical lymphoid cells that predominantly colonize germinal centres of the LNs of the Neck.
- Essential: retained lymph node architecture, with some germinal centres partially or completely replaced by clusters or sheets of plasmablastic, immunoblastic, and/or anaplastic cells; positive immunostaining for LANA (KSHV/HHV8).
- Desirable: positive in situ hybridization for EBV (EBER) and polyclonal B-cell gene rearrangement.

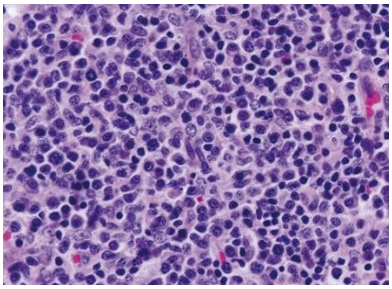
## Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation

### POLYMORPHIC POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER & POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER, NOS



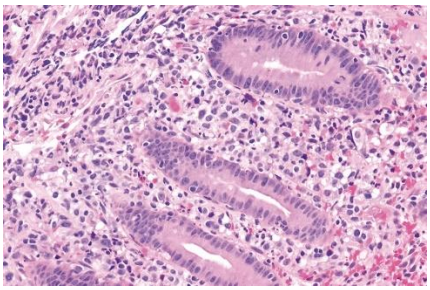
- heterogeneous, non-clonal lymphoid and/or plasmacytic proliferations with preservation of the underlying tissue architecture. They are usually, but not exclusively, driven by EBV or KSHV/HHV8.
- Note: in the posttransplant setting only, it is acceptable to include “posttransplant lymphoproliferative disorder (PTLD)” as an addendum.
- Subtypes: Follicular hyperplasia (FH); infectious mononucleosis–like hyperplasia (IMH); plasmacytic hyperplasia (PCH); KSHV/HHV8-positive multicentric Castleman disease.

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025



- FH shows a normal immunoarchitecture with reactive germinal centres (CD10+, BCL6+, BCL2−). Scattered EBV+ lymphocytes are seen in the interfollicular areas and occasionally within reactive follicles.
- In HIV-related FH, CD8+ T cells are increased within the lymphoid follicles.
- EBV is present in B cells of variable sizes. The immunoblasts and HRS-like cells express CD30, CD45, and IRF4 (MUM1), but typically lack CD15.
- Immunoglobulin light chain protein expression is polytypic in the small and large B cells and plasma cells (which express CD19).
- Typically, hyperplastic lesions are self-limiting and resolve spontaneously, or in some cases may require immune reconstitution.

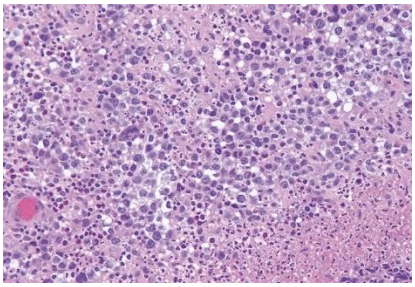
## LYMPHOMAS ARISING IN IMMUNE DEFICIENCY/DYSREGULATION

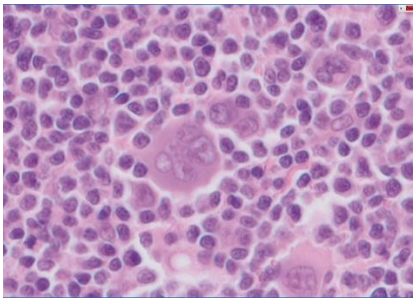


- Lymphomas arising in patients with immune deficiency or immune dysregulation cover a spectrum of lymphoma types.
- EBV and KSHV/HHV8 are associated with a significant proportion of IDD-lymphomas.
- IDD-lymphomas are associated with a large range of clinical features similar to those of corresponding lymphomas in immunocompetent patients, as well as characteristics specific for IDD

**Hodgkin lymphoma**

## CLASSIC HODGKIN LYMPHOMA



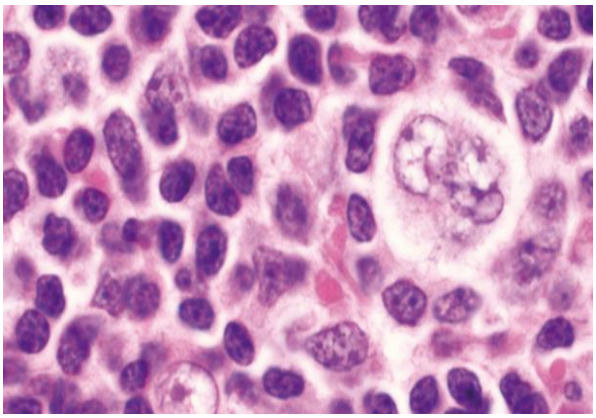


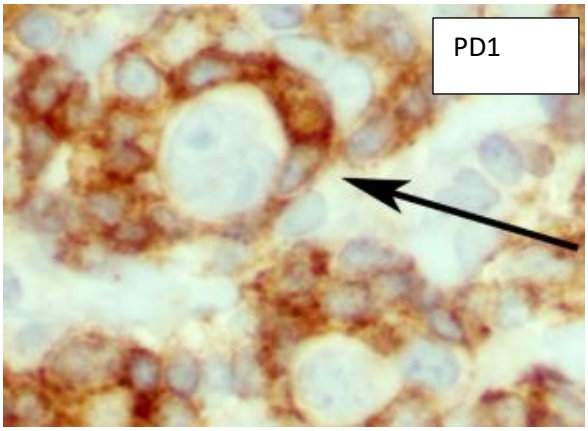
- Classic Hodgkin lymphoma (CHL) is a neoplasm derived from germinal-centre B cells, characterized by a low fraction of tumour cells embedded in a reactive microenvironment rich in immune cells.
- The large neoplastic Hodgkin and Reed–Sternberg cells show a defective B-cell expression program.
- Subtype:
  - Nodular sclerosis classic Hodgkin lymphoma;
  - mixed-cellularity classic Hodgkin lymphoma;
  - lymphocyte-rich classic Hodgkin lymphoma;
  - lymphocyte-depleted classic Hodgkin lymphoma

- IHC: The HRS cells of CHL express CD30 in almost all cases and CD15 in the majority of cases; PAX-5 is Dim; They are usually negative for CD45, CD20 and CD68R. Other B-cell antigens CD19, BOB1 are weak
- Nuclear expression of GATA3 is present in about 80% of CHLs
- Molecular: Because 9p24/CD274/PDCD1LG2 status is important for PD1/PDL1 therapy it is important to assess this locus

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA (NODULAR LYMPHOCYTE PREDOMINANT B CELL LYMPHOMA; AKA NODULAR-LP)

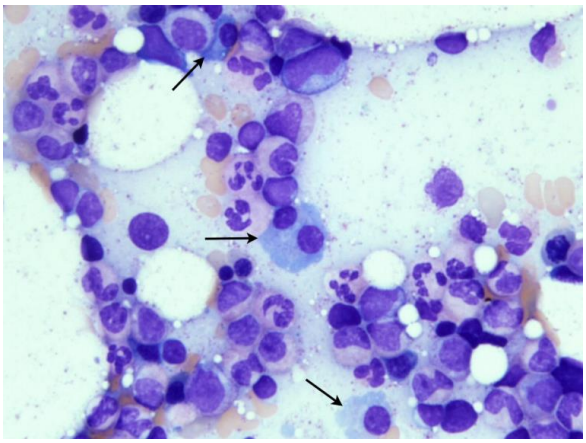





- Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a germinal centre–derived B-cell neoplasm composed of scattered large neoplastic B cells with multilobated nuclei (lymphocyte-predominant [LP] cells) within nodules dominated by mantle zone B cells and follicular dendritic cells (FDCs).
- LNs show partial or complete architectural effacement by a nodular proliferation with or without diffuse areas. Large lymphocyte-predominant cells with multilobated nuclei, pale chromatin, and prominent nucleoli.
- NLPHL with IgD-positive LP cells occurs more commonly in young men
- IHC: LP cells express broad Pan-B markers. Of these **OCT2 is the most reliable marker**. CD19 can be negative
- BCL6, LMO2 and HGAL maybe positive, but CD10 is (-)
- CD30 and CD15 are usually negative
- background TFH cells (PD1-positive) rosetting around tumour cells
- Molecular: LP cells show rearranged immunoglobulin genes and variably express Ig mRNA
- *BCL6* rearrangements in a subset of cases
- Nuclear accumulation of pSTAT6 in LP cells

**Plasma cell neoplasms and other diseases with paraproteins**

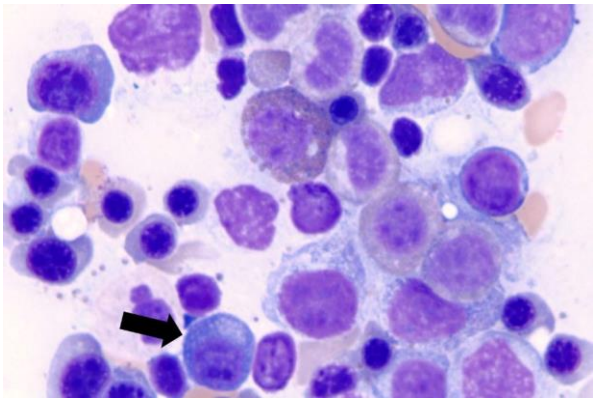
## IGM MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE



- IgM monoclonal gammopathy of undetermined significance (MGUS) is defined by the presence of a serum monoclonal (M) protein of < 3 g/dL, < 10% bone marrow lymphoplasmacytic infiltration (clonal B cells and plasma cells together), and no evidence of anaemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to an underlying lymphoproliferative disorder.
- Histology: Bone marrow shows < 10% clonal involvement by neoplastic cells that are light chain–restricted and exhibit lymphoplasmacytoid or plasma cell differentiation
- IHC: IgM, CD5 (variable), CD19, CD20; and negative for CD10 and CD23
- Molecular: A recurrent mutation, *MYD88* p.L265P, that has been found in > 90% of patients with Waldenström macroglobulinaemia (lymphoplasmacytic lymphoma), can also be present at the MGUS stage.

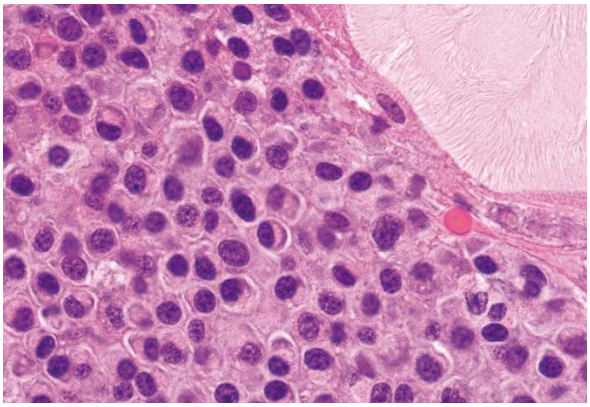
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## NON-IGM MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE



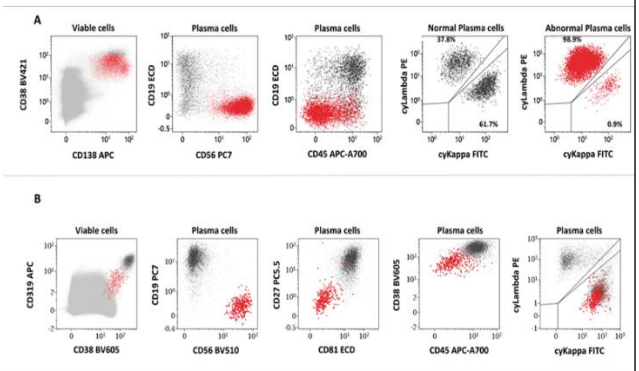
- Non-IgM monoclonal gammopathy of undetermined significance (MGUS) is defined by the presence of a non-IgM (mainly IgG or IgA; rarely IgE, IgD, and light chain only) serum monoclonal (M) protein of < 3 g/dL, clonal bone marrow plasma cells < 10%, and absence of end-organ damage
- Immunophenotype: typically CD38+, CD45 dim to negative, CD19-negative, and CD138-positive.
- FISH studies will reveal the presence of primary cytogenetic abnormalities (t(11;14); t(4;14); t(14;16); hyperdiploidy with trisomies of chromosomes 7, 9, 11, 15, 19) in most patients with an adequate number of plasma cells for analysis.

## PLASMACYTOMA



- Plasmacytoma is a solitary neoplasm of clonal plasma cells without evidence of plasma cell (multiple) myeloma or end-organ damage due to plasma cell neoplasia.
- Rare patients with plasmacytoma have a paraneoplastic syndrome, such as POEMS syndrome
- Subtypes: Solitary plasmacytoma of bone and Extramedullary plasmacytoma (EMP)
- Immunophenotype: similar to that of plasma cell myeloma / multiple myeloma (CD138, CD79a, MUM1), except that expression of cyclin D1 and CD56 is rare or absent. IgG is most common followed by IgA
- The presence of B cells and/or IgM expression suggests B-cell lymphoma with marked plasmacytic differentiation or possibly plasmablastic lymphoma

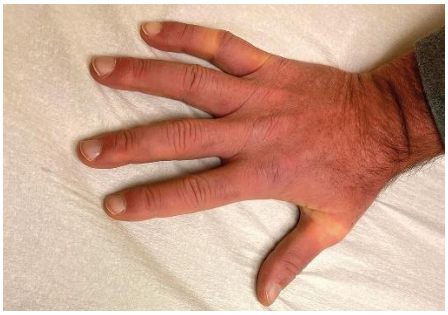
## PLASMA CELL MYELOMA / MULTIPLE MYELOMA




- Multiple myeloma is defined by the combination of plasma cell myeloma, usually associated with a serum and/or urine monoclonal immunoglobulin (Ig), and either evidence of organ damage related to the disease, or in the absence of organ damage, laboratory or imaging findings that suggest a high risk of developing end-organ damage within 2 years.
- Subtypes: Smouldering (asymptomatic) myeloma; non-secretory myeloma; plasma cell leukaemia
- Multiple myeloma–defining biomarkers: bone marrow plasma cells ≥ 60%, ratio of involved to uninvolved serum free light chain (FLC) ≥ 100, and more than one focal bone lesion ≥ 5 mm in size
- IHC: CD38, CD138, VS38, MUM1, CD79a, CD56, CyclinD1
- Cytogenetic:t(4;14), t(6;14); t(11:14), t(14:16), t(14:20)

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

### PLASMA CELL NEOPLASMS WITH ASSOCIATED PARANEOPLASTIC SYNDROME



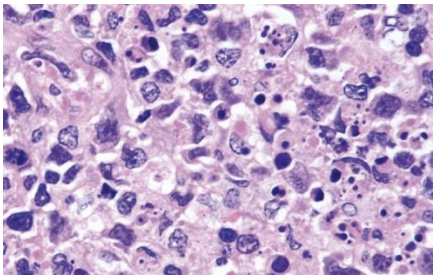
Skin changes, including general rubor and whitening of nails, in a patient with POEMS syndrome.

- This is a group of rare paraneoplastic syndromes associated with plasma cell neoplasms: POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes), TEMPI syndrome (telangiectases, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunting), and AESOP syndrome (adenopathy and extensive skin patch overlying plasmacytoma).
- For the diagnosis of POEMS syndrome, one major criterion and one or more minor criteria must be met, in addition to both mandatory criteria ( polyneuropathy and Monoclonal plasma cell proliferative disorder (almost always lambda)
- For the diagnosis of TEMPI syndrome, all three major criteria ( Telangiectases, elevated erythropoietin, and monoclonal gammopathy IgG Kappa) and one or more minor criteria must be met. Venous thrombosis has been described in a subset of patients and supports the diagnosis.

## T-cell and NK-cell lymphoid proliferations and lymphomas:

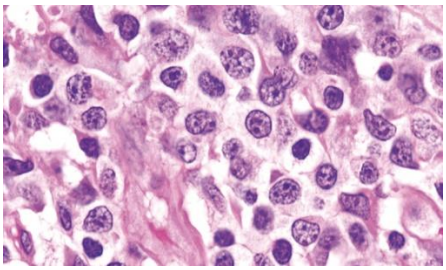
### TUMOUR-LIKE LESIONS WITH T-CELL PREDOMINANCE

### KIKUCHI-FUJIMOTO DISEASE



- Kikuchi–Fujimoto disease (KFD) is a self-limiting disorder characterized by lymphadenopathy with paracortical proliferation of immunoblasts, infiltration by histiocytes with characteristic nuclear features, and apoptosis or necrosis with abundant nuclear debris.
- The involved area can be composed predominantly of histiocytes. The histiocytes show irregular twisted nuclei; some have crescentic nuclei and contain ingested nuclear debris, exuberant T-cells
- IHC: Histiocytes express CD163, CD68, CD4, Dendritic cells CD123 and T-cells CD8 and CD30

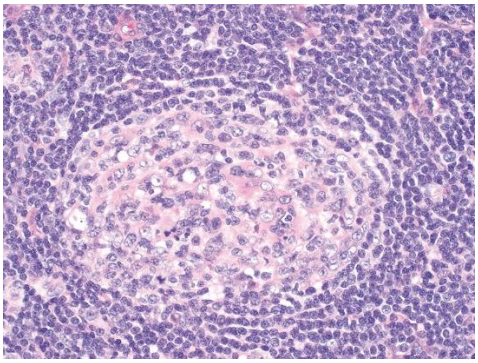
### AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS)



- (ALPS) is an inborn or acquired error of immunity characterized by lymphadenopathy, hepatosplenomegaly, autoimmune cytopenias, and an increased risk of lymphoma. It is associated with germline or somatic defects in the FAS-mediated apoptosis pathway and the accumulation of αβ CD4/CD8 double-negative T cells (DNTs)
- Low-power magnification shows reactive follicles with visible germinal centres and well-formed mantle zones; the paracortex is expanded by a pale-staining lymphoid infiltrate, but the overall lymph node architecture is intact
- The DNTs are positive for CD45RA, CD57 and cytotoxic markers; and negative for CD45RO
- Molecular: FAS, FASLG, CASP8, FADD, or CASP10 mutation

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

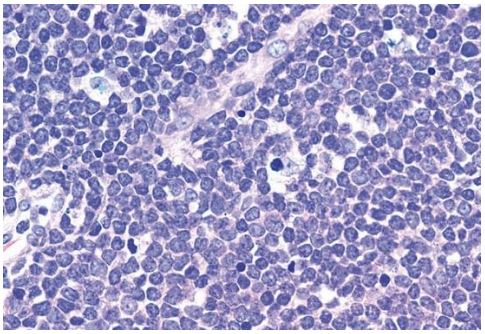
## INDOLENT T-LYMPHOBLASTIC PROLIFERATION



**Precursor T-cell neoplasms**

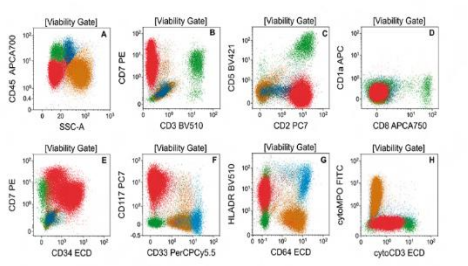
- Indolent T-lymphoblastic proliferation (iT-LBP) is an extrathymic non-clonal expansion of T lymphoblasts occurring alone or in association with other disorders, such as Castleman disease.
- Histology: Sheets of small immature lymphocytes are seen surrounding a reactive follicle but with preservation of normal lymphoid architecture and without invasion into the germinal centers and lack of atypia in the small cells
- IHC: CD3 and TdT. Most cells are double-positive for CD4/CD8; CD2, CD5, CD7, CD10, CD99, and CD1a are variable; high Ki
- Negative stains: CD34, B-cell markers, LMO2
- Molecular: TR gene rearrangements is polyclonal

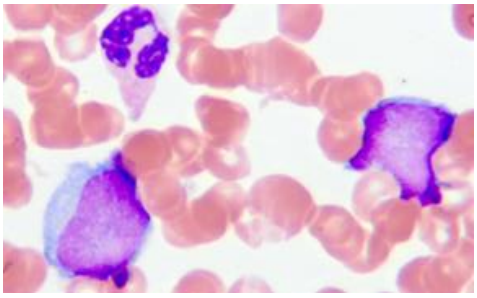
## T-LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA NOS



- T-lymphoblastic leukemia/lymphoma (T-ALL/LBL) NOS is a neoplasm of hematopoietic progenitors committed to T-lineage differentiation and accounts for 15% of childhood ALL.
- Histology: diffuse infiltrate of atypical lymphoid cells with scant cytoplasm and round to irregular nuclear contours. The atypical lymphoid cells display irregular nuclear contours, small nucleoli, and finely dispersed chromatin.
- Immunoprofile: cCD3 (most specific), CD7, CD5, and CD2; CD45 is dim, CD4 and CD8 co-expression, CD1a and CD10 (40% of cases),
- Molecular: clonal rearrangements of the genes TRB and/or TRG in > 90% of cases

## EARLY T-PRECURSOR LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA



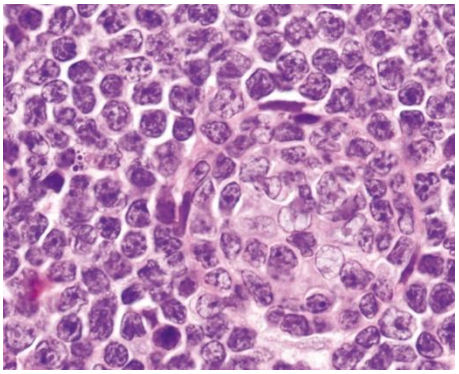



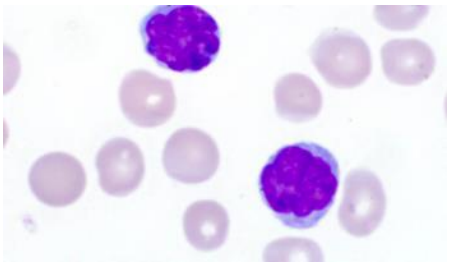
- Early T-precursor lymphoblastic leukemia/lymphoma (ETP-ALL) is a neoplasm composed of blasts committed to the T-cell lineage with a unique immunophenotype that includes the expression of stem cell markers and/or myeloid lineage markers.
- In smears, lymphoblasts are small to medium in size and have round to convoluted nuclei, finely dispersed chromatin, small or absent nucleoli, and mildly to moderately basophilic cytoplasm.
- Histological sections show sheets of lymphoblasts with high N:C ratios, finely stippled chromatin, and inconspicuous nucleoli.
- Immunoprofile: positive for cCD3, absent CD1a and CD8 expression (< 5% positive blasts), absent or dim CD5 expression and expression of one or more myeloid (CD11b, CD13, CD33, CD65, KIT [CD117]) and/or stem cell (CD34, HLA-DR) markers (≥ 25% positive blasts); negative myeloperoxidase.

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## Mature T-cell and NK-cell neoplasms

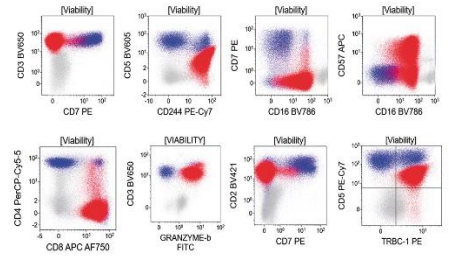
### T-PROLYMPHOCYTIC LEUKAEMIA

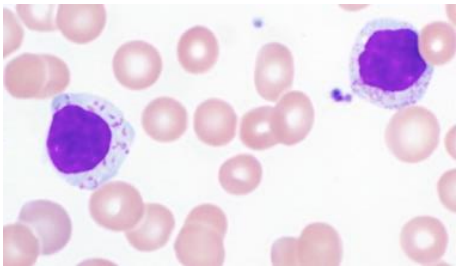




- T-prolymphocytic leukemia (T-PLL) is a clonal proliferation of small to medium-sized prolymphocytes with a mature postthymic T-cell phenotype characterized by the juxtaposition of TCL1A or MTCP1
- Peripheral blood smear: The neoplastic cells are small to medium-sized with irregular nuclear contours, prominent round to oval nucleoli, basophilic cytoplasm, and cytoplasmic blebs.
- Histology: Much of the lymph node is replaced by atypical small lymphoid cells that infiltrate multiple high endothelial venules. A small blood vessel engulfed by small lymphoid cells with oval to irregular nuclei and small but distinct nucleoli.
- Immunophenotype: They are characteristically positive for CD2, CD3 (may be weak), CD5, and CD7, and negative for TdT and CD1a. The neoplastic cells are commonly positive for CD4, with CD4+/CD8− in 40–60%, CD4+/CD8+ in 25–41%, and CD4−/CD8+ in about 15% of cases. Coexpression of CD4 and CD8 is a distinct feature of T-PLL that is rarely seen in other postthymic T-cell neoplasms. **CD52** is usually expressed at a high level and often targeted therapeutically in T-PLL. Overexpression of the oncoprotein **TCL1A** can be detected by IHC and Flow.
- Molecular: Rearrangements involving TCL1 genes (TCL1A, MTCP1) and the T-cell receptor TRA/TRD loci are present in all cases of T-PLL.

### T-LARGE GRANULAR LYMPHOCYTIC LEUKEMIA

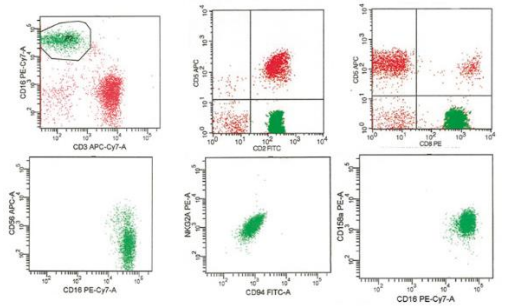


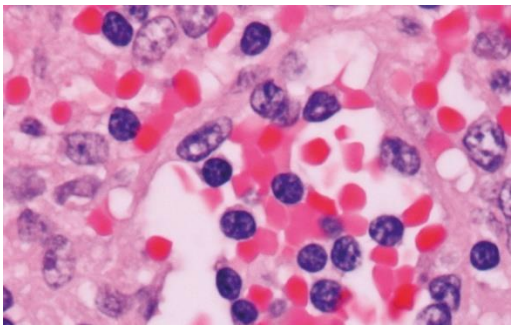



- T-large granular lymphocytic leukaemia (T-LGLL) is a neoplastic proliferation of cytotoxic large granular T cells presenting with persistent absolute lymphocytosis (> 2 × 109/L).
- Peripheral blood smear shows: Small, minimally irregular nuclei with condensed chromatin and abundant pale-staining cytoplasm containing azurophilic granules
- Immunophenotype: Most cases of T-LGLL are of CD8+ αβ T-cell lineage (CD8+ T-LGLL) with a mature effector memory phenotype (CD3+, CD2+, CD8+, CD57+, CD45RA+, CD62L−). A minority of cases express CD4 either alone or in association with CD8dim (CD4+ T-LGLL) . Fewer than 10% of T-LGLL cases are of γδ T-cell lineage; these cases fully express CD57 and CD16, partially express CD8.
- Molecular: Monoclonal TR gene rearrangement and **STAT3 and STAT5B mutations are common**

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

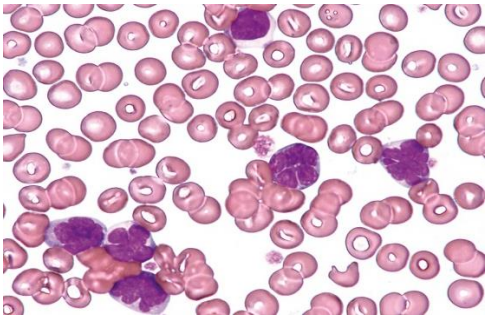
## NK-LARGE GRANULAR LYMPHOCYTIC LEUKAEMIA

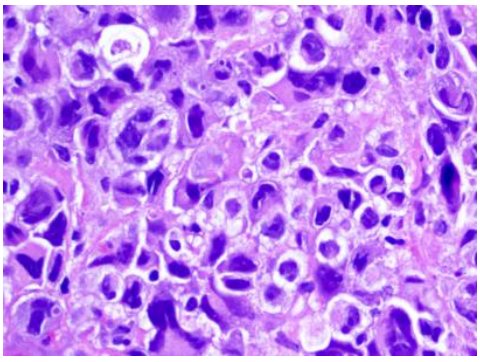




- NK-large granular lymphocytic leukaemia (NK-LGLL) is a neoplasm characterized by a persistent increase in peripheral blood NK cells (usually > 2 × 109/L) and a chronic indolent clinical course.
- **Histology:** The abnormal cells in the blood are usually intermediate to large in size, with abundant pale-staining cytoplasm and variably abundant azurophilic granules. The nuclei are typically small and round, with condensed chromatin and minimally irregular nuclear contours. Look similar to T-LGL
- **Immunophenotype:** Flow cytometry shows that NK-LGLL cells are CD16-positive and sCD3-negative; CD56 is often positive, but approximately 50% of cases show weak or absent expression. Diminished expression of CD2 and CD7 may also be present. Expression of CD8 is variably reported. All cases have abnormal expression of KIR: either a complete lack of detectable KIR or restricted KIR isoform expression is seen
- **Molecular:** Activating mutations of STAT3 affecting the SH2 domain are present in approximately one third of NK-LGLL cases. About 25–30% of NK-LGLL cases have mutations in TET2, and some may have mutations of both TET2 and STAT3

## ADULT T-CELL LEUKAEMIA/LYMPHOMA

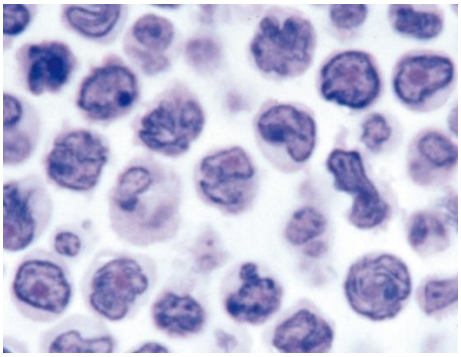




- Adult T-cell leukaemia/lymphoma (ATLL) is a mature T-cell neoplasm associated with HTLV-1 or HTLV-2 and is endemic in Caribbean, middle east, and Africa
- PBS: In the acute subtype, larger atypical cells with lobulated nuclei, namely flower cells, are usually seen
- Immunoprofile: pan–T-cell antigens (CD2, CD3, CD5) but usually lack CD7. Most cases are CD4+ and CD8−, but some are CD4−CD8+, double-positive, or double-negative. **CD25 is expressed in most cases.** Cytotoxic markers are negative. Especially in larger cells, CD30 may be variably positive. Tumor cells frequently express CCR4, and a proportion of cells express FOXP3. Downregulation of CD7 and upregulation of CCR7 and CADM1 are more frequently observed in aggressive ATLL.
- Molecular: Clonal integration of HTLV-1 genome can be demonstrated
- PCR assays are positive for clonal T cell receptor gene rearrangement

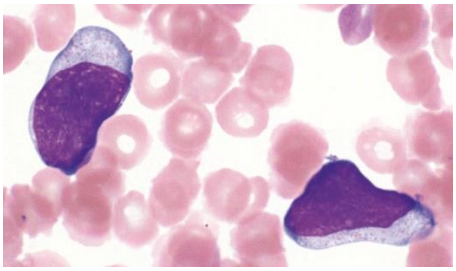
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

### SEZARY SYNDROME



- Sézary syndrome (SS) is a leukemic neoplasm of T lymphocytes, defined by the triad of erythroderma; generalized lymphadenopathy; and the presence of clonally related neoplastic T cells with cerebriform nuclei (Sézary cells) in the skin, lymph nodes, and peripheral blood.
- Histology: The neoplastic cells are medium in size with irregular contours and deep clefts, and they show CD3 expression.
- Immunophenotype: The neoplastic T cells typically show a CD3+, CD4+, CD8– phenotype with frequent aberrant loss of pan–T-cell antigens such as CD2, CD5, CD7, and/or CD26. PD1 (CD279) is expressed by neoplastic cells in skin and blood
- Sézary cells also typically express TCRαβ, CD25, and ICOS, and they sometimes express CXCL13.
- Molecular: TR gene rearrangement analysis
- Essential: an absolute Sézary cell count ≥ 1000/µL, OR an expanded CD4+ T-cell population with a CD4:CD8 ratio > 10

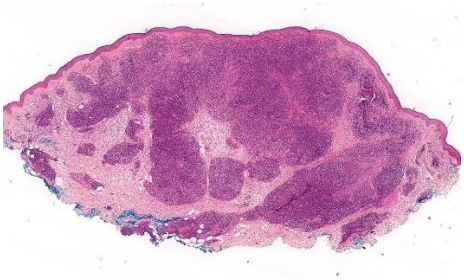
### AGGRESSIVE NK-CELL LEUKAEMIA



- Aggressive NK-cell leukemia (ANKL) is a systemic malignant proliferation of NK cells, with an acute presentation, highly aggressive clinical course, and frequent association with EBV.
- In a peripheral blood smear, the leukaemic cells are very similar to normal large granular lymphocytes with azurophilic granules
- Immunoprofile: The leukaemic cells are typically CD2+, sCD3−, CD3ε+, CD5−, CD7+, CD16+, CD56+, and positive for cytotoxic molecules (granzyme B, perforin, and/or TIA1). CD8 and CD11b may be expressed, whereas CD57 is usually negative. FASL is expressed
- Molecular: Somatic mutations in epigenetic regulators (*DDX3X*, *ARID1A*, histone genes) have been identified. EBV+

## Primary cutaneous T-cell lymphoid proliferations and lymphomas

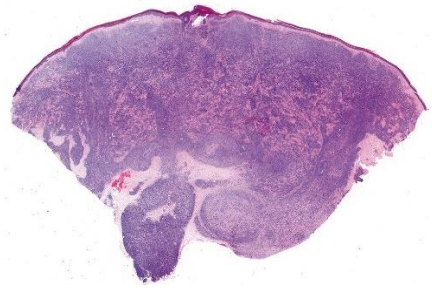
### PRIMARY CUTANEOUS CD4-POSITIVE SMALL OR MEDIUM T-CELL LYMPHOPROLIFERATIVE DISORDER

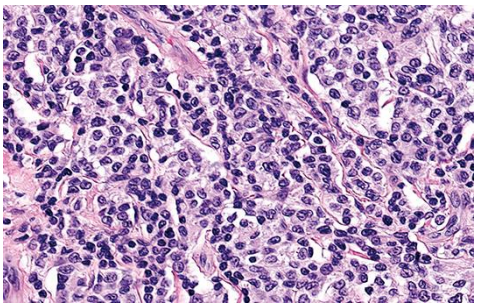


- Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder (PCSM-LPD) characterized by a predominance of small to medium-sized CD4-positive pleomorphic T cells within a solitary skin lesion, without evidence of the plaques typical of mycosis fungoides.
- Histology: Dense Dermal infiltration consisting a predominance of small/medium-sized pleomorphic cells.
- Immunophenotype: CD3+, CD4+, CD8−, CD30− phenotype. The infiltrate is admixed with a B-cell component. PD-1 is positive.
- Molecular: T-Cell Receptor (and less common B-cell) gene rearrangement

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

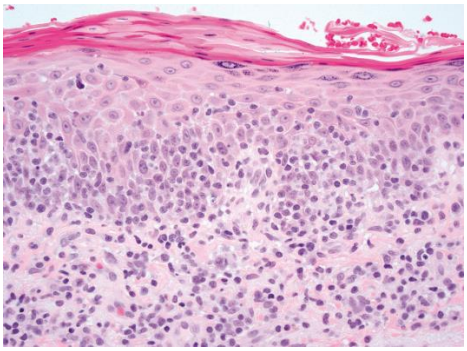
## PRIMARY CUTANEOUS ACRAL CD8-POSITIVE T-CELL LYMPHOPROLIFERATIVE DISORDER





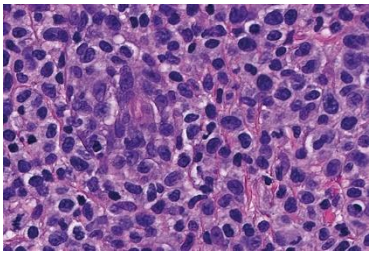
- Primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder is characterized by dermal, non-epidermotropic infiltrates of clonal medium-sized CD8+ cytotoxic lymphocytes, preferentially located at acral sites specially the ears.
- Histology: Low-power magnification shows a dense dermal monotonous infiltrate. Higher-power magnification shows medium-sized tumour cells with moderate nuclear atypia, fine chromatin, and small nucleoli.
- Immunophenotype: CD3+, CD4−, CD8+, CD30−, βF1+, and cytotoxic phenotype, with expression of TIA1, **whereas granzyme B and perforin are usually negative**. Golgi dot-like CD68 expression. EBV is always negative.
- Molecular: clonal rearrangements of TR (TCR) genes

## MYCOSIS FUNGOIDES



- Mycosis fungoides (MF) is a primary cutaneous T-cell lymphoma clinically characterized by the sequential evolution of patches, plaques, and tumours, and pathologically comprising infiltrates of clonal small to medium-sized mature T cells with hyperconvoluted nuclei, which are epitheliotropic in most cases.
- Patch lesion; small atypical lymphocytes migrate into the lower to middle layers of the epidermis and are present in the superficial papillary dermis
- Histology: Plaque lesion. Medium-sized atypical lymphocytes with Pautrier microabscess formation and diffuse, band-like involvement of the papillary dermis
- IHC: Classic: CD2, CD3, CD5, CD4, TCRB, CD45 and CCR4, and loss of CD7, and CD8 negative. Variable CD30 and PD1
- Clinically, classic MF with a cytotoxic phenotype (CD8+ and/or TCRγδ) is also noted
- Molecular: clonal TR gene rearrangement, but of note monoclonal TR gene rearrangement maybe detected in elderly de novo.

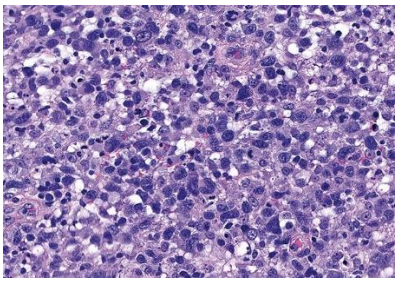
## PRIMARY CUTANEOUS CD30-POSITIVE T-CELL LYMPHOPROLIFERATIVE DISORDER: LYMPHOMATOID PAPULOSIS



- LyP belongs to the spectrum of primary cutaneous CD30-positive T-cell lymphoproliferative disorders. It is characterized by self-healing but recurrent papulonodular skin lesions, atypical CD30-positive T cells by histology, and an excellent prognosis. Negative for ALK
- Subtypes: A, B, C, D, and E; lymphomatoid papulosis with *DUSP22* locus rearrangement
- Histology: Cohesive infiltrates of medium-sized to large lymphoid cells. Expression of CD30 by all atypical cells
- IHC: CD30 (golgi dot pattern), SATB1, CD4 (Subtypes A, B, C) and CD8 in (subtypes D, E, Lyp with DUSP22); Variable TIA1, CD56, and TCRg/d

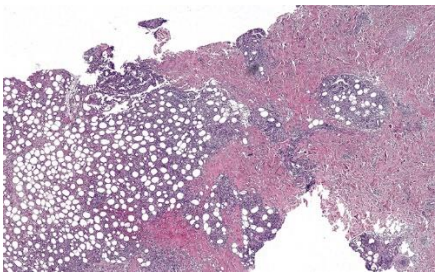
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## PRIMARY CUTANEOUS CD30-POSITIVE T-CELL LYMPHOPROLIFERATIVE DISORDER: PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA



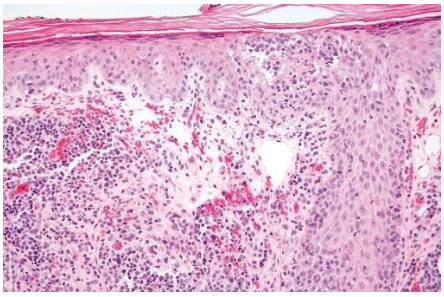
- C-ALCL belongs to the spectrum of primary cutaneous CD30-positive T-cell lymphoproliferative disorders. C-ALCL is composed of large cells with an anaplastic, pleomorphic, or immunoblastic cytomorphology; > 75% of the tumor cells express CD30.
- Histology: Primary cutaneous anaplastic large cell lymphoma. Low-power magnification shows a nodular infiltrate in the dermis and subcutis, without epidermotropism. High-power magnification shows a confluent infiltrate of large anaplastic lymphoid cells
- IHC: CD30 and mostly with an activated CD4 t-cell phenotype, variable loss of CD2, CD3, CD5, and CD7, and frequent cytotoxic proteins. CD15 variable
- Molecular: Vast majority don't have ALK mutation. Rearrangement of DUSP22 has been noted in 25%.

## SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA



- Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a lymphoproliferative disorder predominantly composed of activated cytotoxic medium-sized CD8+ lymphocytes expressing the TCRαβ heterodimer.
- Histology: The infiltrate involves the subcutaneous tissue and spares the overlying dermis and epidermis. Atypical cells rim fat spaces; macrophages are increased in number and contain apoptotic debris. High magnification shows atypical medium-sized lymphocytes with karyorrhectic debris rimming the subcutaneous fat lobules.
- IHC: CD8+ mature αβ T cells (βF1+) and retention of pan–T-cell markers (CD2+, CD5+, CD7+).
-

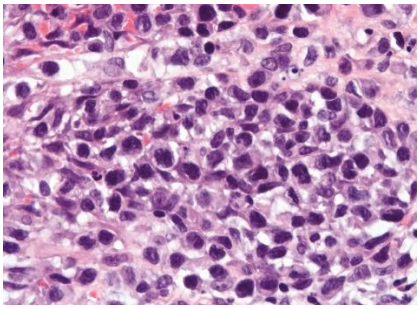
## PRIMARY CUTANEOUS GAMMA-DELTA T-CELL LYMPHOMA



- Primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL) is a clonal proliferation of mature, activated γδ T cells of the Vδ1 or Vδ2 subset, arising within the skin and subcutaneous tissues.
- Histology: Ulcerated plaque of gamma-delta T-cell lymphoma showing a diffuse superficial and dermal infiltrate, with sheets of large atypical lymphocytes, cytotoxic tissue damage, and a large ulcer. The intraepidermal and dermal component shows an epidermotropic and superficial dermal infiltration with cytotoxic tissue changes, haemorrhage, and Pautrier-like microabscesses
- IHC: CD3, CD2, CD7 and CD8 (less expressed); negative for CD4 and CD5; CD56 often expressed. CD30 is positive in minority; EBV negative
- Molecular: TCRγ+, TCRδ+, and TCRβ−

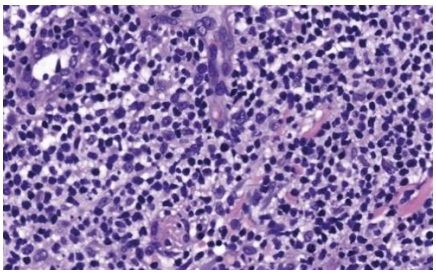
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

### PRIMARY CUTANEOUS CD8-POSITIVE AGGRESSIVE EPIDERMOTROPIC CYTOTOXIC T-CELL LYMPHOMA (PCAETL)



- PCAETL is a neoplastic proliferation of T lymphocytes often expressing CD8 along with cytotoxic molecules, characterized by epidermal necrosis, a high proliferation index, and aggressive clinical behavior.
- Histology: High magnification revealing the presence of a large number of atypical pleomorphic lymphoid cells. The lymphocytes can extend towards the epidermis in a pagetoid fashion and form blisters.
- IHC: CD8, CD3, TIA, Physphorylated STAT3 and STAT5, variable CD2 and CD7
- Molecular: Upregulated JAK2, or gain of function in JAK2, STAT3, and STAT5B; and TCRαβ-expression

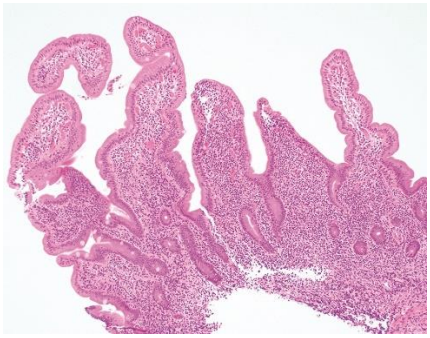
### PRIMARY CUTANEOUS PERIPHERAL T-CELL LYMPHOMA NOS



- Primary cutaneous peripheral T-cell lymphoma (pcPTCL) NOS is a poorly characterized group of T-cell lymphomas not meeting the criteria for any specifically defined primary cutaneous T-cell lymphoma entity; i.e. it is a diagnosis of exclusion.
- Histology: The skin shows diffuse or nodular dermal infiltration of cohesive sheets of mostly medium-sized to large lymphoid cells
- IHC: CD2, CD3, CD4+/CD8- (most common); CD4-/CD8- or CD4+/CD8+ are less common. Cytotoxic markers are negative. Aberrant expression of CD20 can occur. PD1 (40% of cases), High Ki; and EBV negative.
- Molecular/cytogenetic: gains of chromosomes 7q, 8, and 17q and loss of chromosome 9p21 have been reported

## *Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas*

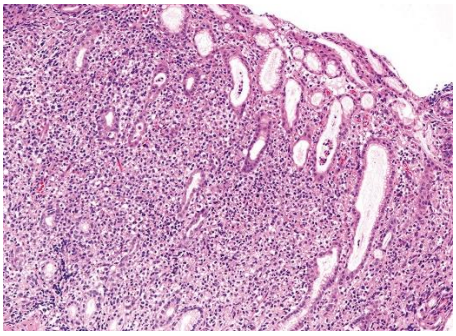
### INDOLENT T-CELL LYMPHOMA OF THE GASTROINTESTINAL TRACT



- Indolent T-cell lymphoma of the gastrointestinal tract (iTCL-GI) is a clonal T-cell proliferation characterized by the infiltration of the lamina propria by small mature lymphocytes lacking significant epitheliotropism, and typically an indolent clinical course.
- Histology: Some of the villi are broadened and the lamina propria is variably expanded by an infiltrate of small lymphocytes. The lamina propria is infiltrated by small lymphocytes that have round or oval nuclei, inconspicuous nucleoli, and scant cytoplasm.
- IHC: CD3, with loss of CD5 and CD7; CD4+ is more common than CD8+; TIA is usually positive but Granzyme is not expressed. EBV (-)
- Molecular: TCRαβ expression

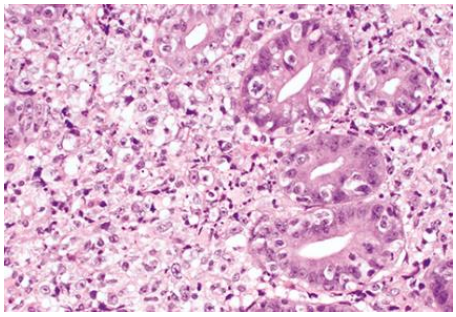
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## INDOLENT NK-CELL LYMPHOPROLIFERATIVE DISORDER OF THE GASTROINTESTINAL TRACT



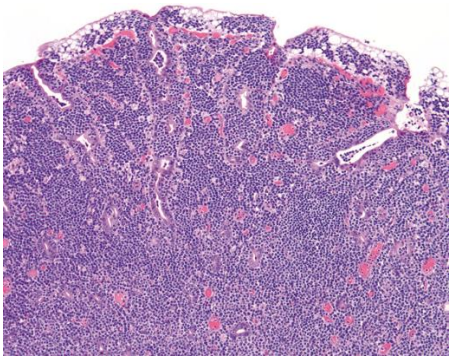
- Indolent NK-cell lymphoproliferative disorder (iNK-LPD) of the gastrointestinal tract is an indolent but recurring EBV-negative NK-cell proliferation that predominantly involves the gastrointestinal tract but occasionally may affect other anatomical sites.
- Histology: mucosal erosion and a dense atypical lymphoid infiltrate composed of medium-sized lymphoid cells with glandular destruction and misplacement.
- IHC: **Strong STAT5 stain**, CD2, CD7, cCD3, CD56, TIA1, and granzymeB; do not express sCD3, TCRαβ, TCRγδ, CD5, CD4, CD8, or CD68. Low Ki and EBV (-)
- Molecular: mutation in JAK/stat pathway; negative EBER and negative clonal TR gene rearrangement

## ENTEROPATHY-ASSOCIATED T-CELL LYMPHOMA



- Enteropathy-associated T-cell lymphoma (EATL) is an aggressive primary intestinal T-cell lymphoma of intraepithelial lymphocytes (IELs), which exhibits variable cellular pleomorphism and usually occurs in individuals with coeliac disease (CD).
- Histology: Infiltration of small intestinal epithelium by enteropathy-associated T-cell lymphoma
- IHC: CD3+, CD5−, CD7+, CD4−, CD8−, CD56−, and CD103+; CD2 expression can vary. Cytotoxic granule proteins (TIA1, granzyme B, perforin) are generally expressed. T-cell receptor expression is mostly absent. Approximately 25% of EATLs are CD8+, and CD30 in large cells, KI is often high, and EBV is negative
- Molecular: ***JAK1* and *STAT3* in EATL;** and *JAK3*, *STAT5B*, and *SETD2* in MEITL
- Note: the presence of *JAK1* and/or *STAT3* SH2 domain hotspot mutations is helpful in differentiating EATL from MEITL

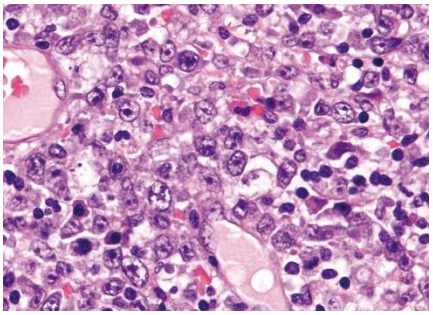
## MONOMORPHIC EPITHELIOTROPIC INTESTINAL T-CELL LYMPHOMA



- Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) is an aggressive primary intestinal T-cell lymphoma of intraepithelial T lymphocytes (MCC in small intestine) , characterized by monomorphic cytomorphology and epitheliotropism, typically lacking association with celiac disease.
- Most frequently encountered are small to medium-sized cells with round or slightly irregular nuclei and dense chromatin. Less frequently, medium-sized cells are admixed with occasional larger cells.
- IHC: CD2+, CD3+, CD4−, CD5−, CD7+, CD8+, CD56+, TIA, and variable perforin, granzyme B.
- Molecular: 47% of cases express TCRγ and 35% express TCRβ; EBER negative

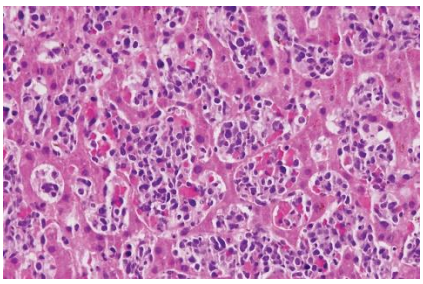
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

### INTESTINAL T-CELL LYMPHOMA NOS



- Intestinal T-cell lymphoma NOS (ITCL-NOS) is an aggressive primary gastrointestinal T-cell lymphoma that lacks the clinicopathological features of defined lymphoma entities arising within the gastrointestinal tract.
- Histology: Large pleomorphic lymphocytes with vesicular nuclei, prominent nucleoli, and scant or moderate cytoplasm
- IHC: CD3 and are usually CD4+ or CD4−/CD8−. Most cases express TCRαβ and a subset are T-cell receptor–silent, TIA, variable CD30/EBV
- Molecular: JAK/STAT and MAPK pathway have been identified in few cases

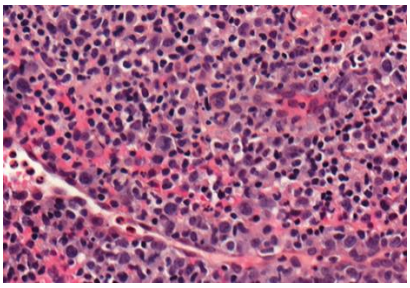
### HEPATOSPLENIC T-CELL LYMPHOMA



- Hepatosplenic T-cell lymphoma is an aggressive mature T-cell lymphoma characterized by a proliferation of cytotoxic T cells within the spleen, liver, and bone marrow.
- Histology: The sinusoids of the liver are extensively involved and expanded by lymphoma cells. Leukemic phase can occur in the late phase
- IHC: positive for CD2 and CD3, they express cytotoxic markers such as TIA1, perforin, granzyme M, and granzyme B (in 30–40% of cases), and they are usually negative for CD4, CD5 and CD8 (~20% positive).
- Molecular: Isochromosome 7q is common; JAK/STAT pathway mutation
- overexpression of NK cell–associated molecules, FOS, VAV3, Syk, and S1PR5. Approximately 75% of cases are positive for TCRγδ, about 20% are positive for TCRαβ, and 5% lack T-cell receptors (silent or null).

## *Anaplastic large cell lymphoma*

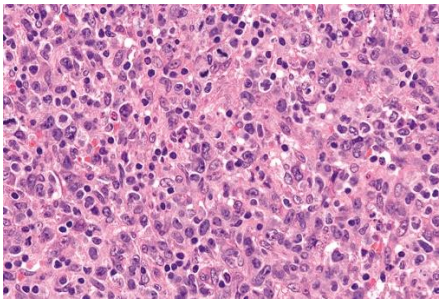
### ALK-POSITIVE ANAPLASTIC LARGE CELL LYMPHOMA



- ALK-positive anaplastic large cell lymphoma (ALCL) is a CD30-positive mature T-cell lymphoma with aberrant expression of ALK secondary to rearrangements of the ALK gene.
- Classic morphology, characterized by a variable number of characteristic hallmark cells with abundant cytoplasm and large horseshoe-shaped nuclei and multiple nucleoli. Monomorphic pattern, comprising uniform large to medium-sized cells.
- IHC: Strong uniform expression of CD30, membrane and golgi area. ALK (NPM1:ALK→ nuclear and cytoplasmic; other ALK variants: membranous. Frequent Pan-Tcell antigen loss, with CD2 and CD4 most expressed. TIA, Granzyme, perforin, CD25 typically expressed. EBV negative
- Molecular: t(2;5)(p23;q35)

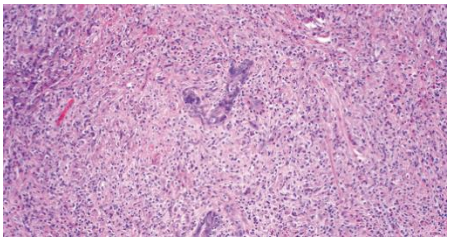
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

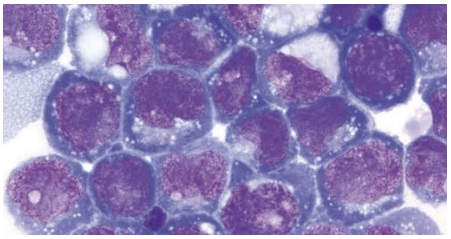
## ALK-NEGATIVE ANAPLASTIC LARGE CELL LYMPHOMA



- ALK-negative anaplastic large cell lymphoma (ALCL) is a mature T-cell lymphoma with uniform strong expression of CD30, without ALK expression or ALK rearrangement
- Diffuse infiltration of large oval cells and scattered hallmark cells; there are frequent mitoses. Pleomorphic cells are admixed with reactive lymphocytes in the background.
- IHC: Uniform CD30, CD43, clusterin, MUM1, and one cytotoxic marker; variable CD4, CD2, CD3, CD5, CD7, and EMA;
- ALK, EBER, and CD8 are negative.
- LEF1 expression is mostly DUSP22 rearranged cases
- Molecular: TR gene rearrangements, DUSP22, TP63, and JACK/STAT mutations.

## BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA

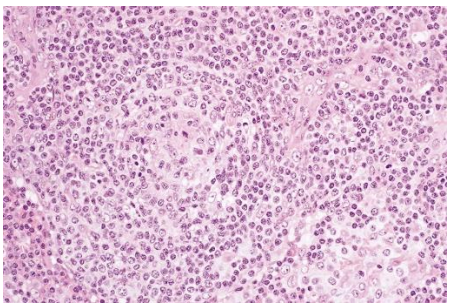




- Breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) is a mature CD30-positive T-cell lymphoma that arises in relation to a breast implant as an effusion confined by a fibrous capsule, and less commonly forming an invading mass.
- Presentation in effusion: large pleomorphic cells in a cytological smear of peri-implant fluid. Lymphoma cells have abundant vacuolated cytoplasm and large multilobated nuclei
- Histology: Tumour cells are found in a background of fibrinous material adjacent to the inner surface of a fibrous capsule
- IHC: The immunophenotype is similar to ALK-negative ALCL with uniform strong expression of CD30. CD3, CD5, and CD7 are usually negative or only focally positive. The neoplastic cells commonly express CD4, CD43, CD25, IRF4 (MUM1), and GATA3
- Molecular: Clonal TR gene rearrangement can be demonstrated in > 80% of cases. BIA-ALCL is consistently negative for gene rearrangements involving *ALK*, *DUSP22*, and *TP63.*

***Nodal T follicular helper cell lymphoma***

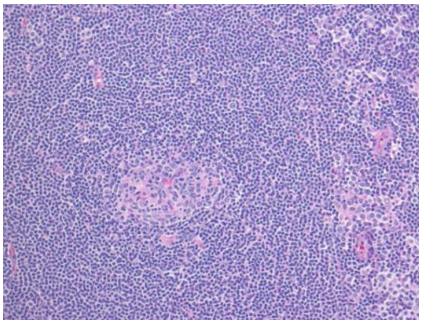
## NODAL T FOLLICULAR HELPER CELL LYMPHOMA, ANGIOIMMUNOBLASTIC TYPE



- Nodal T follicular helper (TFH) cell lymphoma, angioimmunoblastic type (nTFHL-AI), is a neoplasm of mature T cells with a TFH phenotype,
- Histology: partial or complete effacement of the lymph node architecture by a polymorphous lymphoid infiltrate involving lymph nodes, accompanied by a prominent proliferation of high endothelial venules (HEVs) and follicular dendritic cells (FDCs). B-immunoblasts (usually EBV positive) are present in the paracortext.
- Three distinct patterns (1,2,3) are described.
- IHC: positive for the pan–T-cell antigens CD2, CD3,CD4, and CD5, with loss of CD7. CD8 (-). Flow cytometry may reveal dim sCD3. TFH markers PD1 (CD279), ICOS, BCL6, CXCL13, and CD10, expression.
- Molecular: TCR clonal, with RHOA, IDH2, and TET2 mutations

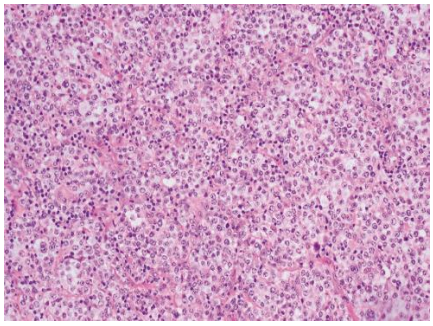
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## NODAL T FOLLICULAR HELPER CELL LYMPHOMA, FOLLICULAR TYPE



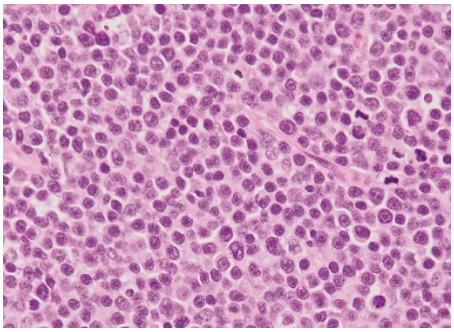
- Nodal T follicular helper (TFH) cell lymphoma, follicular type (nTFHL-F), is a nodal peripheral T-cell lymphoma with a TFH phenotype that displays a follicular growth pattern and lacks the prominent high endothelial venules (HEVs) and extrafollicular follicular dendritic cell (FDC) meshworks characteristic of nodal TFH cell lymphoma, angioimmunoblastic type (nTFHL-AI).
- Histology: Clusters of atypical lymphoid cells with pale cytoplasm
- IHC: positive for the pan–T-cell antigens CD2, CD3,CD4, and CD5, with loss of CD7. CD8 (-). Positive for TFH Markers. CD21→ meshwork
- Molecular: similar to TFHL-AI, with addition of ITK::SYK translocation

## NODAL T FOLLICULAR HELPER CELL LYMPHOMA NOS



- Nodal T follicular helper (TFH) cell lymphoma (nTFHL) NOS is a nodal peripheral T-cell neoplasm with a TFH phenotype, demonstrated by the expression of CD4 and at least two TFH markers, that does not fulfil the required histopathological criteria for nTFHL, angioimmunoblastic type (nTFHL-AI) or nTFHL, follicular type.
- Histology: Diffuse infiltrate of large atypical lymphoid cells, lacking a polymorphous background and or High endothelial venules.
- IHC: CD4-positive and show a minimum of two TFH markers (e.g. CD10, BCL6, PD1, ICOS, and CXCL13)
- Molecular: similar to nTFHL-AI, except that IDH2 mutations are less common

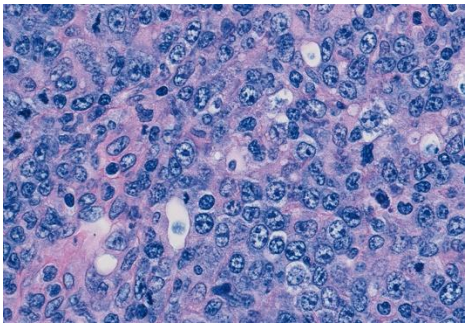
## PERIPHERAL T-CELL LYMPHOMA NOS



- Peripheral T-cell lymphoma (PTCL) NOS is a heterogeneous category of nodal and extranodal mature T-cell lymphomas that cannot be assigned to a specific PTCL entity. Nodal T follicular helper (TFH) cell lymphomas and EBV-positive nodal T- and NK-cell lymphomas are excluded from this category.
- Histology: Most cases comprise medium-sized and/or large lymphoma cells with irregular, pleomorphic, hyperchromatic, or vesicular nuclei; prominent nucleoli; and many mitotic figures.
- IHC: Positive for pan-Tcells with frequent decreased expression of CD5 and CD7. It is more often CD4 positive and TCRa/b. CD56 and CD30 expression can be detected.
- Molecular: PTCL-TBX21 (associated with more cytotoxic antigens) and PTCL-GATA3 molecular subtypes. Also there is often a complex karyotype with gains of 7q and 7p.

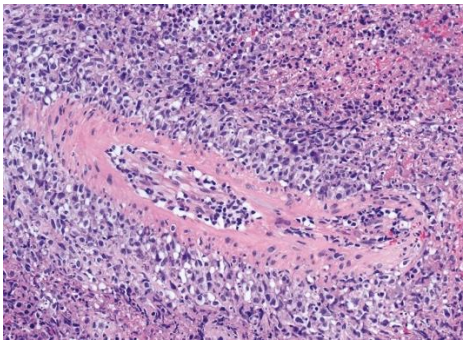
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

### EBV-POSITIVE NODAL T- AND NK-CELL LYMPHOMA



- EBV-positive nodal T- and NK-cell lymphoma is an EBV-positive lymphoma of cytotoxic T- or NK-cell lineage, presenting primarily with nodal disease in adults.
- Histology: mixed population of small, medium, and large cells. The neoplastic cells appear large and pleomorphic, with abundant histiocytes and small lymphocytes in the background.
- IHC: CD3, CD2, and cytotoxic molecules TIA, granzyme B, and perforin. CD8 and CD56 are often positive; CD4 and CD5 are often negative. EBER is positive.
- Molecular: TET2 (64%), followed by PIK3CD (33%), DDX3X (20%), and STAT3 (19%)

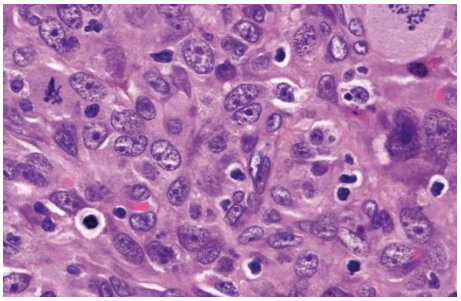
### EXTRANODAL NK/T-CELL LYMPHOMA



- Extranodal NK/T-cell lymphoma (ENKTL) is an extranodal lymphoma of NK- or T-cell lineage that can be divided into two different clinical forms: nasal (80%) and non-nasal (20%)
- Histology: characterized by vascular damage and destruction, prominent necrosis, a cytotoxic phenotype, and an association with EBV.
- IHC: Either Tcell (sCD3) or NK-cell lineage (CD56) and CD2, CD56, EBER, CD7(variable); Other T and NK cell–associated antigens, including CD4, CD8, CD16, and CD57 are usually negative.
- Molecular: EBV by PCR, PRDM1, PTPRK, HACE1, and FOXO3 mutation

## *Stroma-derived neoplasms of lymphoid tissues*

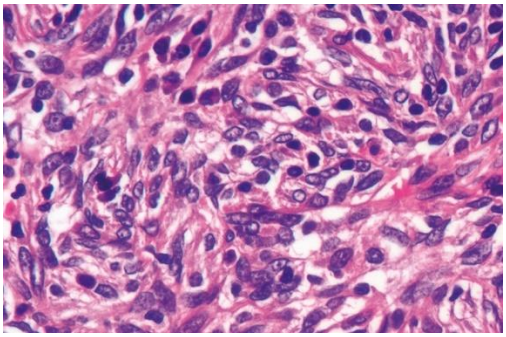
### FOLLICULAR DENDRITIC CELL SARCOMA



- Follicular dendritic cell sarcoma (FDCS) is a malignant neoplasm showing morphological and phenotypic characteristics of follicular dendritic cells (FDCs), which are stroma-derived cells normally found in germinal centres.
- Histology: Tumour cells show ovoid, epithelioid, or spindled morphology. Follicular dendritic cell sarcoma of lymph node: spindled to oval tumour cells have indistinct cell borders and distinct nucleoli; there are intermingled small lymphocytes
- IHC: CD21, CD23, CD35, clusterin, CXCL13, podoplanin (recognized by D2-40), and SSTR2.
- Molecular: recurrent alterations in NF-κB pathway genes (BIRC3, NFKBIA, TRAF3, SOCS3, CYLD, and TNFAIP3) in 40–60% of cases.

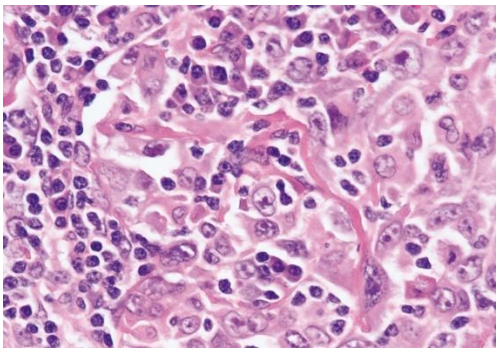
**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

## EBV-POSITIVE INFLAMMATORY FOLLICULAR DENDRITIC CELL SARCOMA



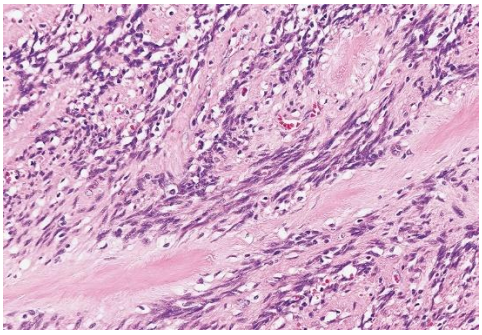
- EBV-positive inflammatory follicular dendritic cell sarcoma (FDCS) is an indolent malignant neoplasm characterized by neoplastic follicular dendritic cell (FDC) proliferation, a prominent lymphoplasmacytic infiltrate, and a consistent association with EBV.
- Histology: The tumour, is accompanied by a rich lymphoplasmacytic component (left field), commonly shows some ectatic blood vessels with fibrinoid deposits.
- IHC: CD21, CD35, CD23, CXCL13, D2-40. LMP1 is usually positive
- Molecular: EBER, copy-neutral loss of heterozygosity of 5q, gain of the X chromosome

## FIBROBLASTIC RETICULAR CELL TUMOUR



- Fibroblastic reticular cell tumour (FRCT) is a neoplasm of putative stromal fibroblastic reticular cell origin.
- Histology: the tumour cells are round or polygonal and have vesicular nuclei and prominent nucleoli. The abundant cytoplasm is eosinophilic. Tumour cells are admixed with many small lymphocytes and plasma cells, and are closely associated with collagen fibres. The cytoplasm of some tumour cells is hyalinized and appears to merge into collagen fibres.
- IHC: Variably positive for actin, desmin, vimenting, cytokeratin, fascin; they lack CD21, CD35, S100, CXCL13.
- Molecular: Not relevant

## INTRANODAL PALISADED MYOFIBROBLASTOMA

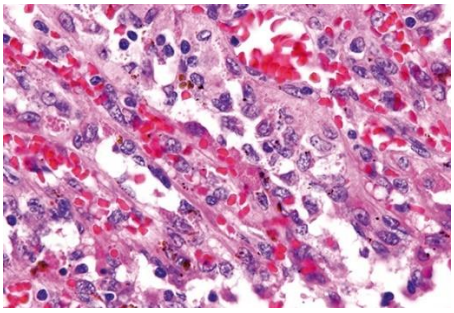


- Intranodal palisaded myofibroblastoma is a benign, lymph node–based smooth muscle / myofibroblastic stromal neoplasm.
- Histology: Elongated collagenous body adjacent to vessels with thickened hyalinized walls. Spindled cells with cytologically bland, elongated nuclei with an occasional longitudinal groove, and scattered rounded, pink intracytoplasmic inclusions.
- IHC: Vimentin, SMA, MSA, Calponin, D2-40, Nuclear B-catenin, cyclinD1; they are negative for keratins, S100, FDC markers
- Molecular: Gain-of-function CTNNB1 exon 3 missense mutations in codon 32, 33, 34, or 37 result in β-catenin–induced upregulation of cyclin D1

**COMPILED BY: ZARRIN HOSSEIN-ZADEH, MD**
*Surgical pathology Fellow/Hematopathology Fellowship*
1/10/2025

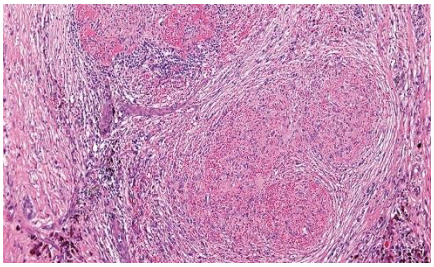
**Spleen-specific vascular-stromal tumors**

### LITTORAL CELL ANGIOMA



- Littoral cell angioma is a benign vascular tumour unique to the spleen, characterized by proliferation of vascular channels with a hybrid endothelial–histiocytic phenotype.
- Histology: The tumour is located within the red splenic pulp and consists of blood-filled, anastomosing vascular spaces reminiscent of normal splenic sinuses. The vascular channels vary greatly in width and some are cystically dilated.
- IHC: tumor cells exhibit vascular markers (ERG, CD31, Factor VIII, and histiocytic markers CD163, CD68, lysozyme). WT1 & CD34 (-). PIRPa (a specific marker), CD207, CD21, claudin-5, VEGFR2 are (+)

### SCLEROSING ANGIOMATOID NODULAR TRANSFORMATION OF SPLEEN



- Sclerosing angiomatoid nodular transformation (SANT) is a benign circumscribed lesion of the spleen composed of multiple angiomatoid nodules with intervening fibrosclerotic stroma.
- Histology: Multiple round or convoluted, sometimes coalescent, angiomatoid nodules occur in a sclerotic background. The individual nodules are surrounded by concentric rings of collagen fibers.
- IHC: Mixed pattern (CD31+, CD8+, CD34−), capillaries (CD31+, CD8−, CD34+), and veins (CD31+, CD8−, CD34−).
- Molecular: *CTNNB1* exon 3 deletions in SANT

### REFERENCES:

*Faiq, A. (2024). WHO classification of tumours. haematolymphoid tumours. International Agency for Research on Cancer*.