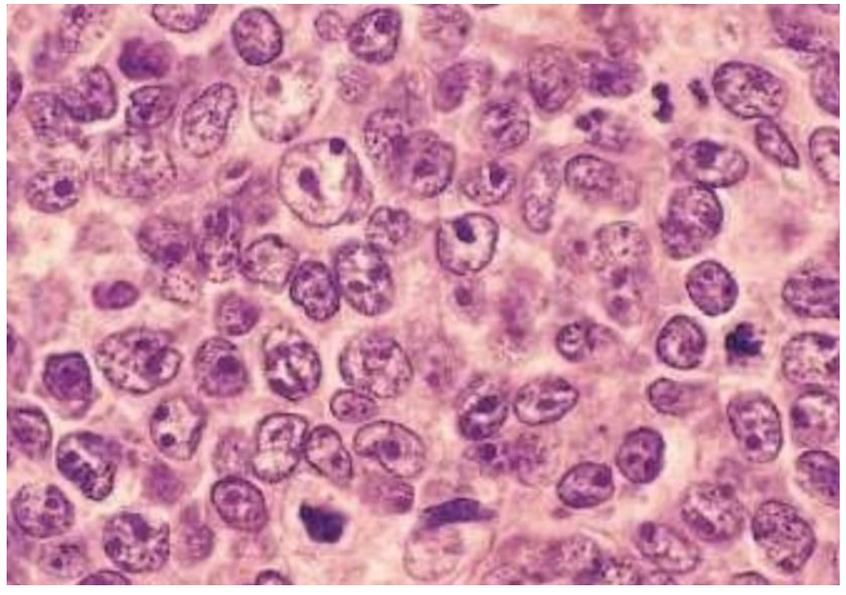
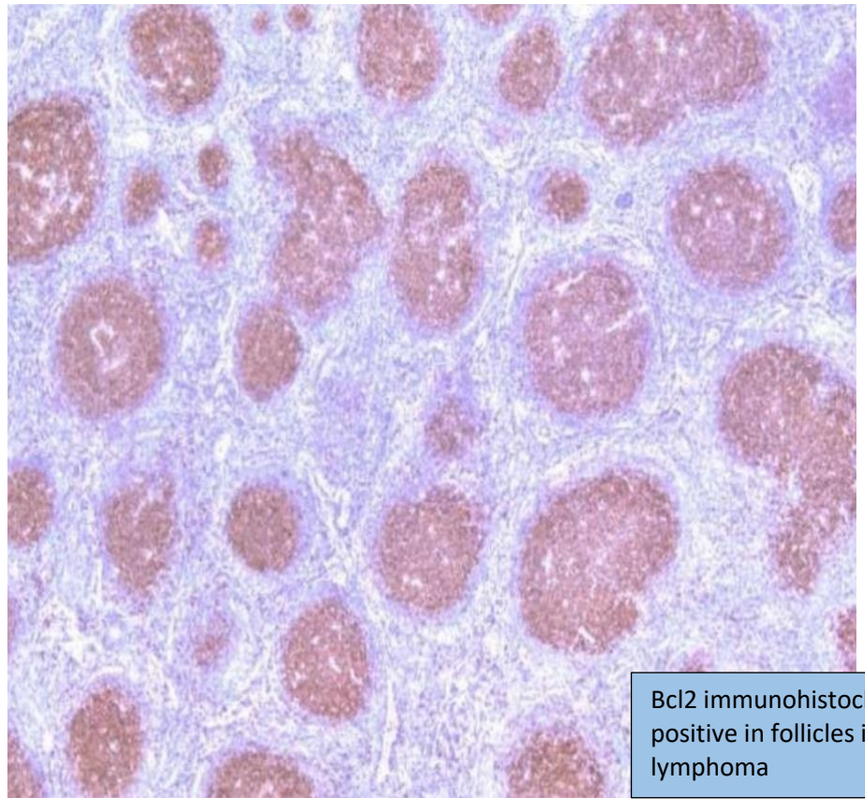
	Diffuse large B-cell lymphoma (DLBCL)	Follicular lymphoma	Burkitt lymphoma	Extranodal marginal zone lymphoma	Mantle cell lymphoma	Small lymphocytic lymphoma (SLL) / chronic lymphocytic leukemia (ALL)		Precursor B and T cell neoplasm		
						Small lymphocytic lymphoma (SLL)	chronic lymphocytic leukemia (CLL)	Lymphoblastic lymphoma	Acute lymphoblastic leukemia	
								B-LL / T-LL	B-ALL	T-ALL
Common in	1.Most common NHL. 2.Predominantly in adults. 3. Most common non-cutaneous extranodal lymphoma (GI most commo)	**1.Second** most common NHL. 2.Common in the West (less in Asian countries). 3.Mainly in > 50 years. 4.M>F.	Most common NHL in **children**	Second most common lymphoma in extranodal sites in adults	Most commonly in older men.	1.SLL represents only 4% of NHL	1.CLL is the most common leukemia in adults	-	the most common childhood malignancy	1.less common. 2. presents in adolescent 3. involving thymus. 4. more common in boys
						2.Affects elderly 3.Not common in Asia				
Grade and prognosis	**High-grade (rapidly growing mass)**	1.Indolent course 2. Overall median survival is 10 years 3.in most cases ,the centrocytes predominate(low-grade) 4. With time, centroblasts increase and the disease becomes high- grade	**Aggressive**	Indolent B-cell lymphoma (indolent means slow)	-	1.Low-grade B-cell neoplasm 2. Variable outcome: many patients have similar survival to general Population (p53 makes the case worse) 3. Richter transformation: predominance of large cells, patients survive <1 year		**Aggressive neoplasms because it affects the precursors.**		
Site of effects & Extranodal and blood involving **All NHLs tend to be Extranodal**	Most common non-cutaneous extranodal lymphoma (GI most common)	1-Patients present with generalized lymphadenopathy. 2-commonly disseminates to BM, liver an spleen (80%)	Extranodal disease: jaw (endemic) enlargement of jaw because the involvement of salivary glands in EBV pathogenesis, terminal ileum, retroperitoneum, ovary, CNS (sporadic), sometimes leukemic	As the name implies, it is Extranodal lymphoma	1.Affects LNs,Waldeyer ring. 2.Commonly involve BM, blood in 20%, sometimes in GIT, appears as submucosal nodules (**lymphomatoid polyposis**)	Can arise in **LNs and solid tissue (SLL)**, or in **BM and peripheral blood (CLL)**. 50% have generalized lymphadenopathy and hepatosplenomegaly		Lymphoblastic lymphoma when occurs in solid tissue (T>B)	Acute lymphoblastic leukemia when circulates peripheral blood and involve bone marrow (B>T)	
								-	B-ALL tends to disseminate to solid organs (brain, testis, spleen)	-
Infiltration	-	-	-	**Infiltrate the epithelium and causes destruction**	-	-		**leukemic infiltration** in the solid organs		
Subtypes	1)Primary mediastinal large B-cell lymphoma: arises from thymic B-cells, most patients are middle age women, spread to CNS and visceral organs	2)EBV-associated DLBCL: arise in immune suppressed patients and in elderly, begin as polyclonal B-cell proliferation	3)Human Herpes Virus-8: causes DLBCL in pleural cavity, encodes cyclin D1 mimicker protein, seen in immune suppressed patients	-	-	-		-		
Mutations	1.2/3 have activating mutation of Bcl6 promotor gene, which is an important regulator of gene expression in germinal center B- cells. 2. 30% have t(14;18) (Bcl2 → IgH) which results in overexpression of Bcl2 protein (anti-apoptotic. 3. Few has mutation in MYC gene	1-t(14;18) (Bc12 → IgH) Overexpression of Bcl2 results in prolonged survival of lymphoma cells. 2-1/3 of patients have mutations in genes encoding histone- modifying proteins (epigenetic change)	1-t(8;14) MYC→IgH Overexpression of MYC transcription factor, potent regulator of Warburg metabolism (aerobic glycolysis)	-	1-t(11;14) that fuses cyclin D1 gene to IgH locus Overexpression of cyclinD1, promote progression of cell cycle	1.deletion mutation in genes encoding micro-RNAs that are negative regulators of Bcl2 and that will cause increased Bc12 protein. 2. A surface immunoglobulin called B-cell receptor (BCR), is autonomously active, activating a intermediary called Bruton tyrosine kinase (BTK) that activates genes promoting cell survival. 3 Chromosomal translocation is rare.		Mutations in transcription factors for genes responsible for maturation of blasts. Mutations in RAS signaling and tyrosine kinase proteins promoting cell survival.		
								mutation in PAX5 gene	70% have mutations in NOTCH1 gene	1.**Most childhood B-ALL have:** a.hyperdiploidy (>50 chromosomes). b.t(12;21), involving ETV6	T-ALL shows mutation in PTEN gene (tumor suppressor) and CDKN2A (promotes cell cycle)

									and TUNX1 genes, creating new transcription factors. 2. Adult B-ALL exhibits: a. t(9;22) between ABL and BCR genes, similar to chronic myeloid leukemia, creating a new tyrosine kinase protein (imatinip)	
Original cells	Germinal center B cell	Germinal center B cell	B-cells of germinal center origin	B- cell	naïve B-cells in mantle zone	B-cell		lymphoblasts, the most immature lymphoid cell		
								B-cell precursor	T-cell precursor	B-cell precursor	T-cell precursor
Cell markers of malignants	CD20 , Bc12	CD20, Bc16, Bc12	CD20 , Bc12			CD20, Bcl2 , CD5		CD34 , TDT			
Morphology	cells are large (3x normal lymphocytes), irregular nuclei, small nucleoli, frequent mitosis	1.The normal architecture of lymph node is effaced by nodular proliferation (follicles). 2.The follicles are composed of: -small irregular “cleaved” lymphocytes “centrocytes”. -large lymphocytes with vesicular nuclei and small nucleoli (multiple nucleoli)”centroblasts”	Size: intermediate Monomorphic (uniform) Shape: round/oval Nucleoli: multiple+small Cytoplasm: lipid vacuoles Very high mitosis (brisk mitotic activity) Tingible body macrophages engulfing nuclear debris	-	small centrocytes, but in diffuse pattern	1.LN: effacement of architecture. 2. (small in size and round in shape). 3. Dark chromatin 4. few large cells with central prominent nucleolus (prolymphocyte) 5. Proliferation centers: focal areas containing large number of prolymphocytes and increased mitosis	1.Leukemic cells appear similar to lymphocytes. 2. Occasional prolymphocytes 3. Smudge cells.	-		1.Blasts are large, high N/C ration. 2. Chromatin is open (pale). 3. Nucleolus sometimes Present. 4. Cytoplasm is not granular
Clinical features	-	-	-	-	-	1-Many patients are asymptomatic. 2-Leukocytosis can reach very high levels (>200,000). 3-50% have generalized lymphadenopathy and hepatosplenomegaly 4-Immune dysfunction is common, by suppressing normal B-cells, resulting in hypogammaglobulinemia (50% of patients) 5-Anemia: 15% of patients develop auto antibodies against RBCs and platelets (cold type), secreted by normal B-cells 6-Thrombocytopenia: similar to ITP		1.Anemia 2.Thrombocytopenia 3.Damage to solid organs secondary to leukemic infiltration		
Other associated conditions and complications	1.Most cases arise de novo 2.few complicate a previous low-grade B-cell lymphoma 3.some associated with EBV and herpes virus 8	40% develop transformation to DLBCL (worse than de novo DLBCL)	1.Endemic + sporadic associated with EBV 2.Immunodeficiency associated with HIV and other immunodeficient conditions.	1.Arises in the setting of chronic inflammation. 2.Can complicate autoimmune disease in localized areas (Hashimoto thyroiditis, Sjogren syndrome).		-		-		

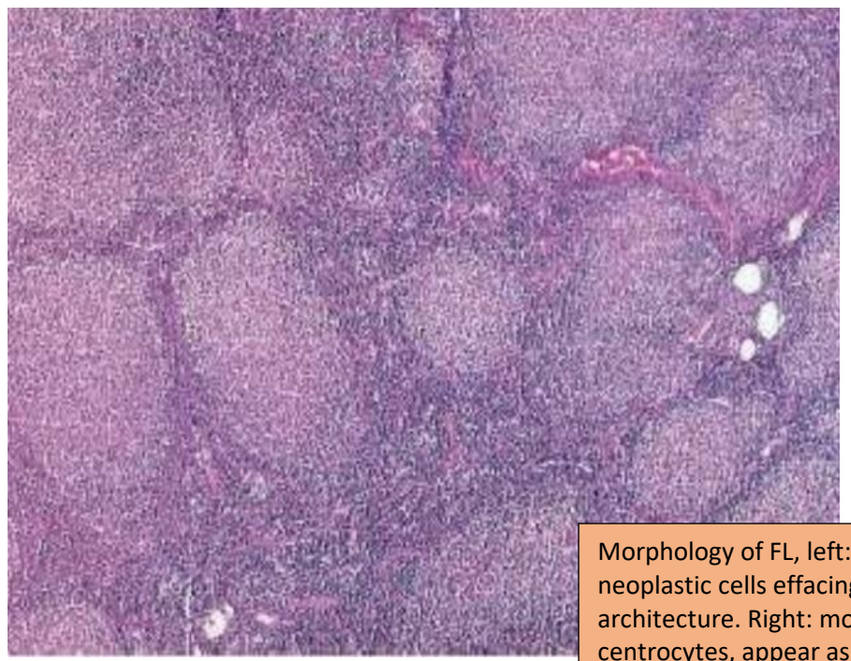
				3.Can complicate Helicobacter pylori-chronic gastritis.					
Favorable prognostic factors	-	-	-	-	-	-	-	1.hyperdiploidy. 2.low WBC count 3.age between 2-10 years	-
Poor prognostic factors	-	-	-	-	-	1.P53 mutation makes prognosis worse 2.Richter transformation: predominance of large cells, patients survive <1 year	-	1.age < 2 years, 2.age in adolescents or adults 3.WBC count >100k	-
Treatment	-	1.Conventional chemotherapy is ineffective 2. Therapyisreservedtosymptomaticpatients,bulky tumors and transformation (**cytotoxic chemotherapy, anti-CD20, anti-Bcl2**)	-	-	-	-	-	-	-

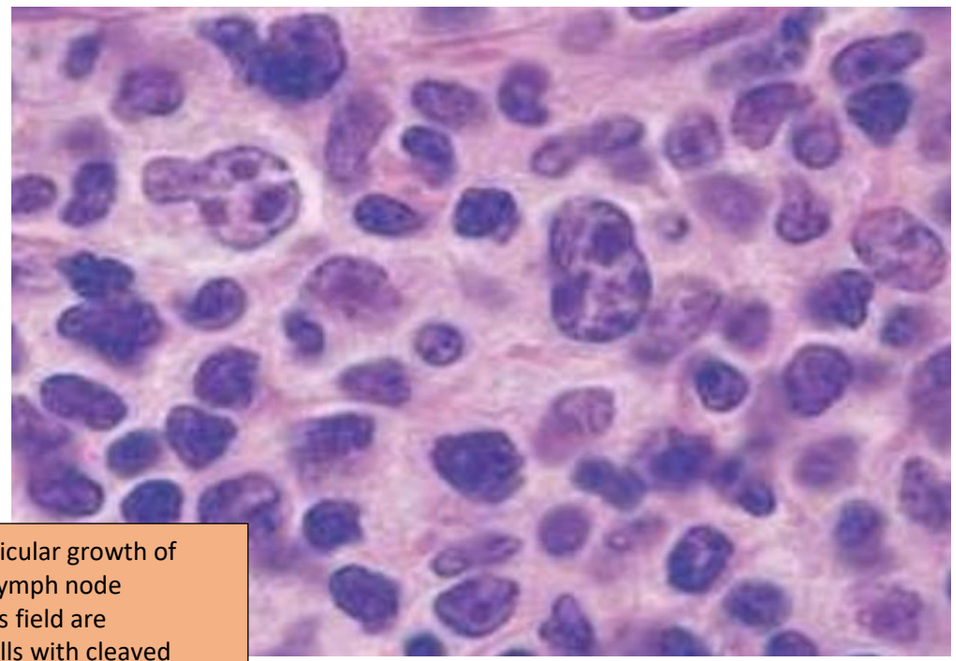


DLBCL: cells are large (3x normal lymphocytes), irregular nuclei, small nucleoli, frequent mitosis. Positive for CD20

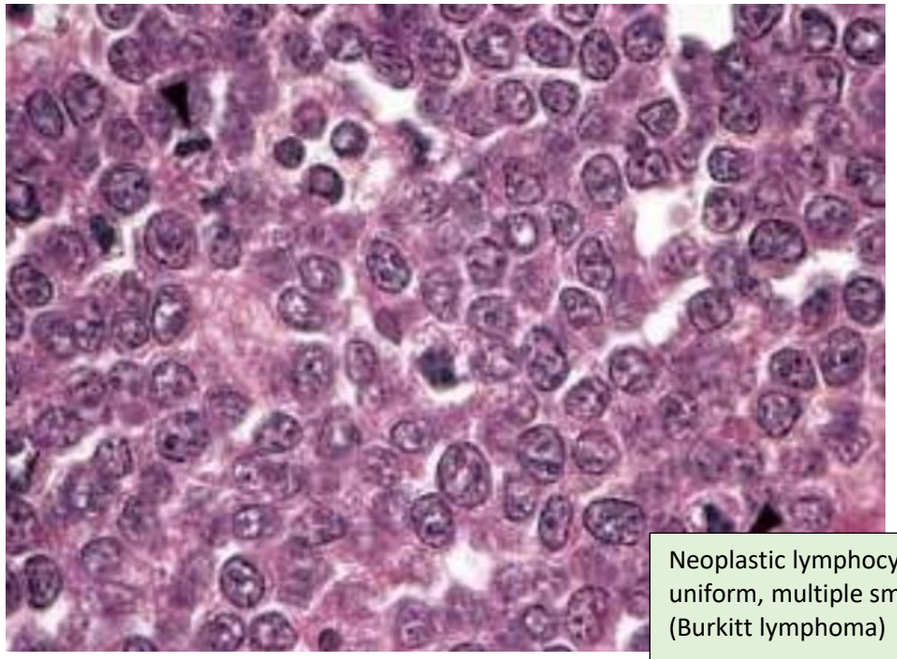


Bcl2 immunohistochemical stain is positive in follicles in follicular lymphoma

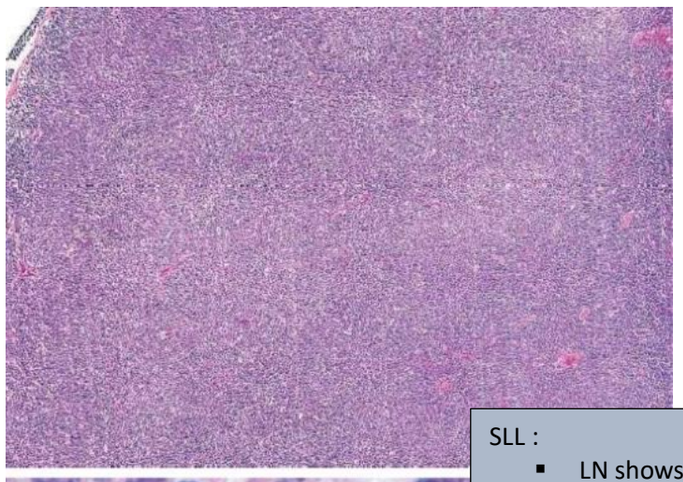


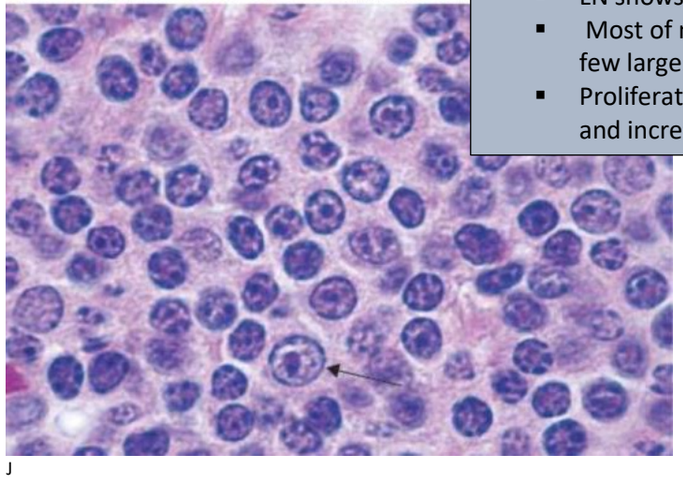


Morphology of FL, left: nodular (follicular growth of neoplastic cells effacing the entire lymph node architecture. Right: most cells in this field are centrocytes, appear as small fark cells with cleaved nuclei. There are few large cells with multiple nucleoli, corresponding to centroblasts



Neoplastic lymphocytes are monotonous and uniform, multiple small nucleoli, brisk mitosis (Burkitt lymphoma)





SLL :

- LN shows effacement of architecture
- Most of neoplastic cells are small in size, round, dark chromatin, along with few large cells with central prominent nucleolus (prolymphocyte)
- Proliferation centers: focal areas containing large number of prolymphocytes and increased mitosis

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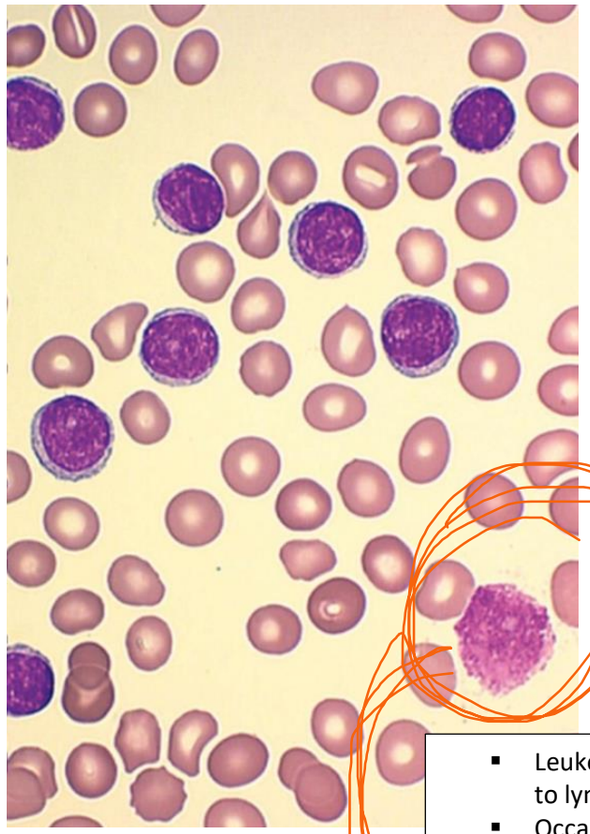

- Leukemic cells appear similar to lymphocytes
- Occasional prolymphocytes
- Smudge cells