

Small Cell Lymphoma

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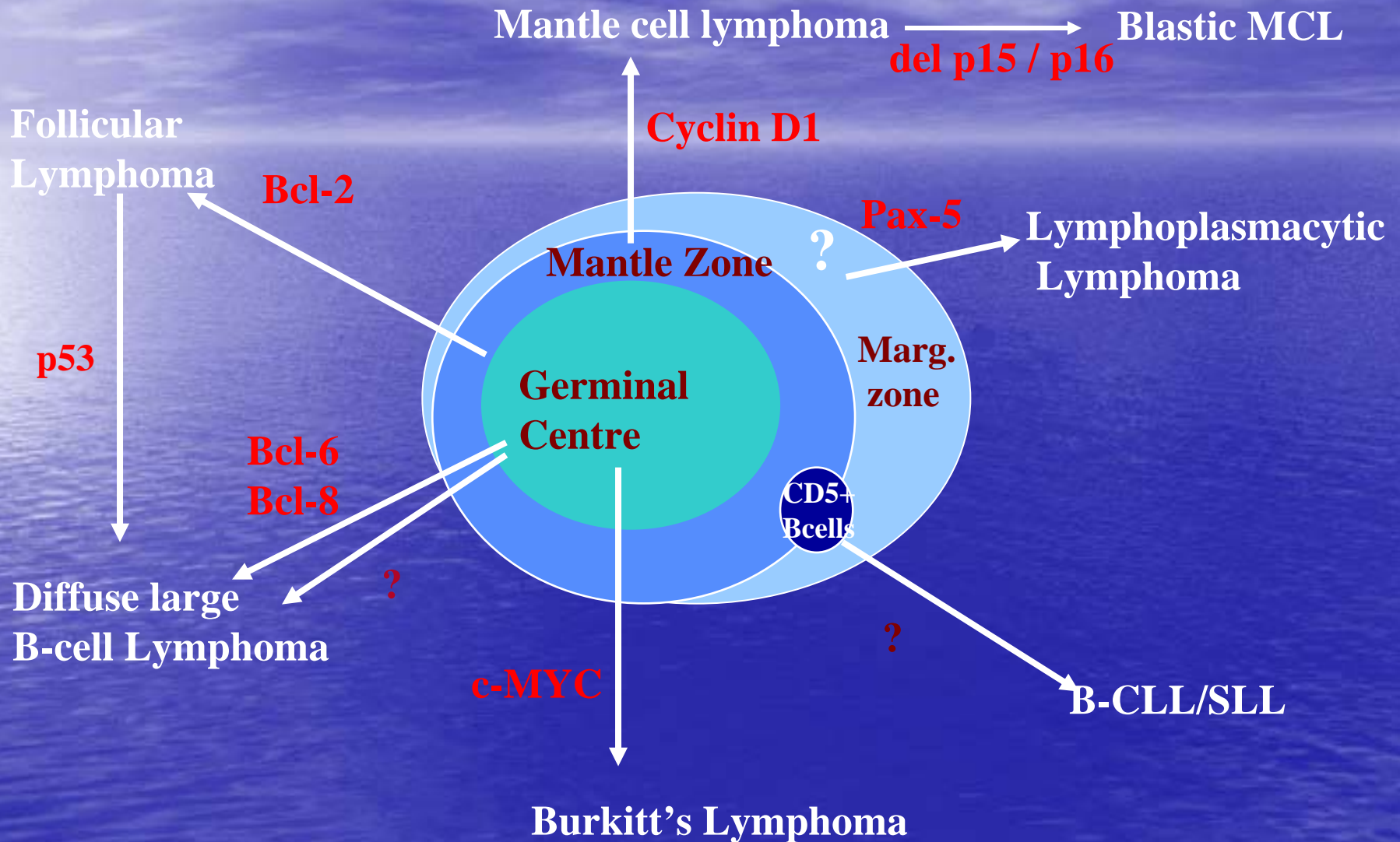
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WHO Classification (2001)

- B -cell neoplasms
- T-cell and NK –cell neoplasms
- Hodgkin lymphoma

Molecular Pathways of B-cell Lymphoma genesis



Small Cell Lymphoma

- WHO classification 2001: a group of B cell neoplasms that develop from mature (i.e. peripheral) B-lymphocytes.
- The different subtypes appear to recapitulate stages of B cell differentiation.

Small Cell Lymphoma

- Chronic lymphocytic leukaemia (CLL)/
Small lymphocytic lymphoma (SLL)
- Lymphoplasmacytic lymphoma (LPL)
- Follicular Lymphoma (FL)
- Mantle Cell Lymphoma (MCL)
- Marginal Zone Lymphoma (MZL)

Small Cell Lymphoma Incidence

Relative incidence varies widely:

USA: 50% of all non-Hodgkin Lymphomas

Middle East: 12%

Geographic variation in the distribution of major NHL subtypes (%)

Subtypes	USA	Europe	South Africa	Middle East	India	Oriental counties
CLL / SLL	7	5-11	8	1	5	1-3
FL	32	11-28	33	7	15	7-8
MCL	7	7-14	1	0	5	1-3
MZBL	6	3-13	4	4	4	10-21
DLBCL	28	25-36	28	59	33	36-47
BL	2	3-4	2	13	4	1-2
T-LL	2	0-1	2	4	7	1-4
PTCL	3	4-8	8	2	5	9-10
ALCL	2	0-2	3	7	4	1-4
NK/T cell	0	0-2	0	0	0.5	3-9

	CLL	IC	HCL	PCM	MZL	SMZL	MCL	FL
Ig	Faint sIgM+ sIgD+/-	cIgM +	sIgM	cIg	sIgM+ & sIgD- cyto Ig-/+	sIgM+ & sIgD+ cyto Ig-/+	sIgM+ & sIgD+	sIg+
CD20	+	+	+	-/+	+	+	+	+
CD10	-	-	-	-/+	-	-	-/+	+
CD5	+	-	-	-	-	-	+	-
CD43	+	+/-	+	-/+	-/+	-/+	+	-
CD23	+	-/+	-	-	-	-	-	-/+
CD11c	-/+	-/+	+	-	+/-	+/-	-	-
CD103	-		++	-	-	+	-	-
CD138	-		-	+	-	-	-	-
Bcl-6	-		-	-	-	-	-	+
Cyclin D1	-	-	+/-	-/+	-	-	+	-
IgHv	M/U	M	M	M	M	M	U	O

**Chronic lymphocytic leukaemia (CLL)/
Small lymphocytic lymphoma (SLL)**

Chronic lymphocytic leukaemia: leukemic form of disease

Small lymphocytic lymphoma: solid organ disease: 10 to 20% progress with time to CLL.

CLL; WHO classification, 2007

- Monoclonal B-cell lymphocytosis: clonal lymphocytes in PB < 5000/cumm with aberrant phenotype
- CLL has two major variants: may derive from either immunoglobulin V(H) gene unmutated (naïve) or mutated (antigen-experienced) post-germinal center B-cells (ZAP-70 negative).

CLL

- Develop from circulating CD23 +ve, CD5+ve, IgM & IgD +ve lymphocytes found in primary lymphoid follicles and mantle zone of reactive secondary follicles
- They express CD20 (weak), CD79a (strong), CD23, CD5 and weak SIg

CLL/ SLL

- Stain positively for CD20, CD79a, CD23, CD5 , BCL2, and express weak SIg
- Stain negatively for CD3, CD10, BCL6, CD38, CD138, MUM1.

CLL/ SLL

- Lymph nodes show complete effacement by diffuse lymphoma infiltration with pale “proliferation centres” present in 80 to 90% of the cases.
- Spleen involvement is mainly seen in the form of white pulp infiltration.
- Marrow infiltration can be nodular, interstitial or diffuse in pattern

CLL/ SLL: Diagnosis

- CLL: is often diagnosed by bone marrow/ peripheral blood findings & flowcytometry
- CLL by flowcytometry; this uses a scoring system according to cells positivity for B-lymphocytes antigens and surface Ig:
- Scoring markers/ 1 point each: weak SIg, CD5, CD23, weak CD79b/CD22 and negative FMC7

Diagnostic CLL score: 4-5.

CLL/ SLL: uncommon features

- nuclear irregularity of the lymphoma cells &/ or negative staining for CD5 or CD23

Should suggest the possibility of mantle cell lymphoma

- plasmacytoid differentiation

Should exclude lymphoplasmacytoid lymphoma

☐ Other Differential: AML, ALL and other Small CL

CLL; WHO classification, 2007

- Cytogenetic alterations are important in prognosis of CLL; 80% of cases have abnormal karyotyping.
- Deletion at 13q14 is found in 50% of the cases, imply long survival
- Trisomy 12 found in 20% of cases usually show unmutated Ig V gene region (aggressive clinical course)

CLL; WHO classification, 2007

- Richter's transformation: a term defines a clinical situation in the evolution of CLL.
- Usually related to CLL cases with mutated Ig V gene region.
- 3-10% of CLL cases develop Richter's transformation (DLBCL); Immunophenotypically, most cases of DLBCL irrespective of clonal relationship to CLL show significant differences in phenotype compared with the B-CLL, with common loss of CD5 and CD23.
- 10 to 20% of SLL progress with time to CLL

Richter's transformation of chronic lymphocytic leukemia. The possible role of fludarabine and the Epstein-Barr virus in its pathogenesis.

Thornton PD,

et al. *J Leuk Res.* 2005 Apr;29(4):389-95.

Transformation of CLL into a large cell lymphoma has an incidence of 3-5%. Studied 101 cases of CLL treated with fludarabine over a 10-year period (1990-2000) and observed a 12% incidence of transformation. In six of 12 patients, transformation was documented within 4 months following treatment with fludarabine.

Richter's transformation in chronic lymphocytic leukemia.

Tsimberidou AM, Keating MJ., Semin Oncol. 2006 Apr;33(2):250-6.
Department of Leukemia, The University of Texas M. D. Anderson
Cancer Center, Houston, TX 77030, USA.

Richter's syndrome develops in 3.9% of cases of CLL.

The large cells of RS may arise through transformation of the original CLL clone or represent a new neoplasm.

RS may be triggered by viral infections, such as Epstein-Barr virus (EBV).

Trisomy 12 and chromosome 11 abnormalities, as well as multiple genetic defects, have been described in patients with RS.

The median overall survival duration at our institution of patients with RS is 9.1 months

CLL/ SLL: prognostic features

- proliferation index (Ki-67) < 25% have a significantly better prognosis
- > 10% of prolymphocytes in marrow aspirate is suggestive of an aggressive clinical course
- P53 expression (10%)
- CD38 expression



Lymphoplasmacytic Lymphoma

Lymphoplasmacytic lymphoma (LPL); WHO classification 2007

- LPL is a neoplasm of small B lymphocytes, plasmacytoid lymphocytes and plasma cells, usually involving bone marrow, lymph nodes and spleen. Usually CD5-ve and may have a serum monoclonal protein.
- Plasmacytoid/cytic variants of other lymphomas should be excluded (CLL, MCL, FL and MALT lymphoma).
- Waldenstrom's macroglobulinemia is a subset of LPL with IgM gammopathy of any concentration.

Lymphoplasmacytic lymphoma

- This lymphoma usually involves bone marrow, lymph nodes and spleen.
- Lymphoma infiltration is diffuse
- Some of the cells would show cytoplasmic (Russell bodies) or nuclear inclusions (Dutcher,s bodies). Reactive histiocytes can be numerous.

Lymphoplasmacytic lymphoma (LPL)

- Positive: CD20, CD79a & for plasma cell antibodies (CD38, CD138 and MUM-1)
- Positive for surface and cytoplasmic Igs
- Negative: (CD5 -/+), CD23 (CLL) and CD10 (FL)
- Differentiation from MZL with plasma cell differentiation can be difficult

Lymphoplasmacytic lymphoma (WHO Classification 2007)

- Proposed diagnostic criteria for WM:
- IgM monoclonal gammopathy of any concentration
- Bone marrow infiltration by LPL cells
- Exclude other Ig producing lymphomas mainly CLL, MCL, FL, SMZL
- A small percentage of LPL cases transform to diffuse large B cell lymphoma.



Follicular Lymphoma (FL)

Follicular Lymphoma (FL)

- Neoplasm of follicle centre B lymphocytes, that recapitulates both the architecture and cytological features of normal secondary follicles.
- Incidence: ranges from 7% in Middle East to 20% in Western Europe to 35% in USA
- Median age is 59 years
- Male: female= 1:1.7

Follicular Lymphoma (FL)

- Lymph nodes show complete or partial replacement by nodular infiltration
- The follicles are often uniform, smaller than reactive follicles with a smaller mantle zone.
- Polarity of follicles is absent and only small areas of paracortex are usually seen
- Diffuse areas are common and often associated with bands of fibrosis

Follicular Lymphoma (FL)

- Lymphoma cells are composed of a mixture of centrocytes and centroblasts
- They express B lymphocyte antigens (CD20, CD79a), GC antigens (CD10 and BCL-6) and BCL-2
- Networks of FDC are demonstrated by CD21 and CD23

Follicular Lymphoma (FL)

Differential Dx

- Reactive lymphadenopathy: polarity, paracortex, mantle zone, BCL2, CD10
- Colonization of follicles by other lymphomas: MCL, MZL, LPL
- Diffuse LBCL; 25% of grade 3 FL are –ve for BCL-2 protein; use other markers (CD21, CD10, BCL-6) and analysis of t(14;18) by FISH

Follicular Lymphoma (FL)

- **Grade 1** 0-5 centroblasts per HPF (x400)
- **Grade 2** 6-15 centroblasts per HPF
- **Grade 3** >15 centroblasts per HPF
 - 3a: Centrocytes present
 - 3b: Solid sheets of centroblasts with no centrocytes

Follicular Lymphoma (FL): reporting

- Grade: 1, 2, 3a or 3b
- Proportion of follicular and diffuse areas
 - Predominantly follicular when follicular area is >75% of the whole lymphoma
 - Follicular and diffuse when follicular component makes 25 to 75% of the lymphoma
 - Predominantly diffuse when follicular component makes < 25% of the lymphoma.
- Any component of DLBCL

Grading of F. Lymphoma

- Reproducibility of grading FL is difficult among expert pathologists (60-70%)
- The number of large cells in FL is a continuum
- Clinical data re grading vs prognosis is contradictory
- Current therapeutic strategies do NOT discriminate between grade 1-3a.
- Proposal (WHO 2007): FL G1-3a and FL G3b

Follicular Lymphoma (FL)

25 to 30% of cases transform to DLBCL during their clinical course

Follicular Lymphoma in situ

- Diagnosed in reactive lymph nodes where a few germinal centres express Bcl-2/ t(14/18).
- Make sure that the Bcl-2 staining is not related to excess of T lymphocytes.
- FL in situ can be found in de novo reactive lymph nodes and in those close to nodes with FL
- Cong et al: Blood:99:3376-82, 2002: diagnosed 13 cases; 3 of them developed into FL after about 10 years of follow up

Light-chain-restricted germinal centres in reactive lymphadenitis: report of eight cases.

Nam-Cha SH, et al. Histopathology. 2008 Mar;52(4):436-44.

- six cases of persistent reactive lymphadenitis were analysed
- In all cases, some germinal centres contained a population of plasma cells and plasmacytoid germinal centre cells showing light chain immunoglobulin restriction.
- In three cases the monotypic cells also showed distinct Bcl-2 expression.
- One of the patients developed a follicular lymphoma, which became evident from a subsequent biopsy

Paediatric FL

- Morphology: Large irregular follicles resembling PTGC
- Usually Grade 3
- Positive: CD10 and Bcl-6; Negative: Bcl-2
- Genetics: t(14;18) is absent
- Clinically: Stage 1 with nodal or testicular presentation
- Often cured by surgery or chemotherapy
- Rare Bcl-2 positive cases (aggressive)

FL of the intestine

- Small bowel, often duodenum
- Bcl-2 +ve, often IgA +ve, t(14;18) +ve
- Indolent disease
- Often accidental finding
- Spontaneous regression is reported



Mantle Cell Lymphoma

Mantle Cell Lymphoma (MCL)

- is a diffuse B cell neoplasm composed of monomorphic small to medium sized lymphocytes with cytological appearance of centrocytes (cleaved cells)
- is the equivalent of “pure centrocytic lymphoma” in the Kiel classification
- develops from a CD5 positive peripheral B lymphocyte found in mantle zone of lymphoid follicles

Mantle Cell Lymphoma (MCL)

- represents 3-10% of lymphoma cases
- thought to be rare in the Middle East
- usually affects older patients with average age of 60 years
- male to female ratio of 2:1
- predominantly a lymph node disease

Mantle Cell Lymphoma (MCL)

- The neoplastic cells resemble centrocytes of germinal centres (? centrocyte type 2)
- They are small to medium in size and contain irregular cleaved nuclei with inconspicuous nucleoli
- No other cell types are seen, except reactive T cells and histiocytes

Mantle Cell Lymphoma (MCL)

Histological variants can mimic:

- CLL
- Large cell lymphoma “Blastoid” variant where there is a high mitotic index
- May colonize reactive follicles and therefore can be confused with FL
- Follicular variant shows diffuse expansion of mantle zone associated with relative preservation of germinal centres
- About 25% of patients show lymphocytosis; such cases can be confused with prolymphocytic leukaemia.

Mantle Cell Lymphoma (MCL)

- stain positive for B lymphocyte antibodies (CD20 & CD79a), BCL-2 protein, CD5 and for surface IgM.
- stain negative for CD23, germinal centre markers (CD10 & BCL-6) and plasma cell antibodies
- Stain negative for T cell markers (CD2, CD3, CD4, CD8) except CD5

Mantle Cell Lymphoma (MCL)

- positive staining for Cyclin D1 is seen in more than 80% of the cases of MCL
- in positive cases, All lymphoma cells should stain positive
- is the most reliable marker of MCL.
- staining for Cyclin D1 should be used regularly in lymphoma diagnosis
- Cyclin D1 positivity varies in different Labs
- FISH analysis: all cases of MCL demonstrate chromosome 11;14 translocation and also overexpression of Cyclin D1 messenger RNA

In-situ mantle cell lymphoma--a report of two cases.

Agel N, Barker F, Patel K, Naresh KN.

Histopathology; January 2008; volume 52; pages: 256-260

Cyclin D1 Negative MCL

Cyclin D1-negative mantle cell lymphoma: a clinicopathologic study based on gene expression profiling.

Fu K, et al (Lymphoma/Leukemia Molecular Profiling Project).

Blood. 2005 Dec 15;106(13):4315-21

The clinical, pathologic, and genetic features of 6 cases of cyclin D1-negative MCL.

All 6 cases exhibited the characteristic morphologic features and the unique gene expression signature of MCL but lacked the t(11;14)(q13;q32) by fluorescence in situ hybridization (FISH) analysis.

The tumor cells also failed to express cyclin D1 protein, but instead expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases).

There was good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis.

Patients with cyclin D1-negative MCL were similar clinically to those with cyclin D1-positive MCL.

In conclusion, cases of cyclin D1-negative MCL do exist and are part of the spectrum of MCL. Up-regulation of cyclin D2 or D3 may substitute for cyclin D1 in the pathogenesis of MCL.

Indolent MCL, WHO 2007

- A indolent form of MCL has been recognised with long survival (18-144 m).
- Most of the cases have been diagnosed retrospectively
- Usually non-nodal disease, leukemic phase is common, splenomegaly may appear later
- None of the above are predictive of indolent MCL

Is B-PLL an entity?

Definition: PLL $>55\%$ prolymphocytes in PB without t(11,14).

B-prolymphocytic leukaemia with t(11;14) revisited: a splenomegalic form of mantle cell lymphoma evolving with leukaemia.

Ruchlemer R, Parry-Jones N, Brito-Babapulle V, Attolico I, Wotherspoon AC, Matutes E, Catovsky D.

Br J Haematol. 2004;125: 330-6

Marginal Zone Lymphoma (MZL)

- a B cell lymphoma which comprises three distinct anatomical and histological subtypes: Splenic MZL, Extranodal MZL of MALT type and nodal MZL
- accounts for about 7% of all cases on NHL
- Arises from B lymphocytes of “marginal zone”; an area found surrounding reactive secondary follicles, rich in “monocytoid B lymphocytes”

Marginal Zone Lymphoma (MZL)

- Lymphoma cells are composed of a mixture of small centrocyte-like cells, small lymphocytes, monocytoid cells, and centroblast and immunoblast-like cells, in addition to cells exhibiting plasma cell differentiation.

Marginal Zone Lymphoma (MZL)

- Positive for B lymphocyte antigens (CD20 & CD79a)
- Lymphoma cells show light chain restriction, is helpful in differentiating MALT lymphoma from inflammatory conditions in primary epithelial organs.
- Express surface immunoglobulins (IgM & IgD in splenic MZL) and IgM and IgA or IgG in MALT lymphoma
- They are negative for small cell lymphoma markers (CD5, CD10, CD23, BCL-6 and Cyclin D1)
- Negative for T cell antibodies (CD3, CD2, CD4 & CD8)

