

# Follicular Lymphoma (FL) Pathology

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**F**ollicular lymphoma (FL) is the most common type of low-grade B cell lymphoma seen in western countries. It is characterized by a clinically indolent course. The cellular origin of the neoplastic cells are follicular center B lymphocytes<sup>[1]</sup>. The incidence of FL in eastern countries is low.

FL predominantly involves the lymph nodes, but spleen, bone marrow, peripheral blood, and Waldeyer's ring involvement have also been reported. The gastrointestinal tract, soft tissue and skin are the most commonly involved extranodal sites.

Histologically, FL is composed of centrocytes and centroblasts, and usually has a follicular growth pattern. Neoplastic follicles are often ill-defined, and lack mantle zones. When the mantle zones are preserved there could be difficulty on differentiation from reactive follicular hyperplasia. Interfollicular infiltration of the neoplastic cells is a helpful diagnostic criterion for the cases having this morphology. Diffuse pattern may be seen and it is thought to be of clinical significance. In the WHO classification, FL is graded as 1, 2, 3a, and 3b according to the number of centroblasts per high-power field<sup>[1]</sup>. Histological grade correlates with prognosis in FL, with grades 1 and 2 being indolent and grade 3 being more aggressive. In grade 3 FL, the presence of a diffuse component is commonly seen and some studies have demonstrated that this finding is correlated with a worse outcome<sup>[2]</sup>. Presence of residual reactive follicles within the involved lymph nodes could reflect the stage of the disease<sup>[3]</sup>.

Cases of 'in situ localization of FL' have been reported in the literature<sup>[4]</sup>. It appears to represent early microscopic involvement of FL within the lymph nodes. The clinical significance of these cases without other evidence of lymphoma is not known yet<sup>[4]</sup>.

The tumor cells are positive for CD19, CD20, CD22, CD79a, surface Ig (IgM+/IgG-, IgG or rarely IgA), bcl-2, CD10, and bcl-6 and negative for CD5, CD43, CD23 and Cyclin D1<sup>[1]</sup>. Immunohistochemistry is very useful for the diagnosis of FL, and several studies revealed the relation of expression of various proteins with clinical outcome. The proliferation index of the cells within the neoplastic follicles by MIB-1 (Ki-67) provides a measure of proliferative rate, and has been shown to correlate with FL grade but has limited prognostic significance in some studies. Some recent data revealed that proliferation index may have prognostic value in FL<sup>[5]</sup>. High Ki-67 staining in the reactive lymphoid follicles is useful for the differentiation of reactive follicular hyperplasia and FL. The proliferation index of the neoplastic follicles in low grade FL (grades 1 and 2) is lower than in reactive follicular hyperplasia and grade 3 FL. But in a recent study of Wang et al., high proliferation index in low grade FL was determined in nearly 20% of their cases. The clinical behavior of these low grade FL cases showing high proliferation index was correlated with inferior disease-specific survival but higher five-year disease free rate similar to grade 3 FL<sup>[6]</sup>.

Although most patients with FL overexpress Bcl-2 protein, higher levels of expression have been correlated with worse outcome. In contrast, higher levels

of expression of germinal center markers including CD-10, Bcl-6 and PU.1 have been correlated with a favorable outcome.<sup>[7,8]</sup> The presence of more than 15 CD68+ macrophages per high power field has also been shown to predict for a poor outcome.<sup>[9]</sup>

The genetic hallmark of FL, t(14;18)(q32;q21), which juxtaposes the bcl-2 gene with the IgH gene, is seen in 80-90% of FLs<sup>[10]</sup>. It is not associated with the prognosis. Bcl-2 protein is expressed in the majority of the cases, and its expression reduces as histological grade increases. Although FL is rarely seen in pediatric patients, it should be noted that bcl-2 expression in pediatric FL is relatively infrequent in contrast to its adult counterpart<sup>[10, 11]</sup>. Primary cutaneous follicle center cell lymphoma is accepted as a variant of FL and is often bcl-2-negative as well<sup>[12, 13, 14]</sup>.

A number of cytogenetic abnormalities have been described in FL, including p53 mutations, loss of p16, upregulated MYC expression resulting from translocation or other mechanisms, gains of chromosome arms 7p or 7q, Xp, 12q and 18q, as well as losses on 6q and possibly mutations of bcl-2 and/or bcl-6 genes. The presence of additional genomic aberrations, in particular 17p and 6q deletions, is more frequent in grade 2 and 3 FL patients and correlated with shorter survival and a higher rate of transformation into diffuse large B cell lymphoma<sup>[10,11]</sup>.

Approximately 25-35% of FL cases transform into diffuse large B cell lymphoma as well as Burkitt's lymphoma, precursor B lymphoblastic lymphoma and classical type of Hodgkin's lymphoma<sup>[1, 15-17]</sup>.

**Molecular prognostic markers examined for follicular lymphoma.**<sup>[10, 11, 15-17]</sup>

Prognostic Marker	Effect on Outcome	Mechanism
-Chromosomal gains +7, +12q13-14, +18q	Unfavorable	Dominant oncogenes
-Chromosomal losses Del6q, -9p21, -17p13 gene	Unfavorable	Loss tumor suppressor
-BCL-6 translocation	Unfavorable	Genomic instability
-Bcl-2 expression	Unfavorable	Anti-apoptotic
-Bcl-6 expression	Favorable	Germinal center phenotype
-CD10 expression	Favorable	Germinal center phenotype
-PU.1	Favorable	Germinal center phenotype
-Macrophage content microenvironment	Unfavorable	Modulation by
-MDM2 expression	Unfavorable	Functional p53 loss
-Bcl-XL	Unfavorable	Anti-apoptotic
-Cyclin B1	Favorable	Cell cycle progression
-Immune response microenvironment (IR-1 versus IR-2)	Variable	Modulation by
81-gene predictor	Variable	Reflects tumor behavior

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