Follicular Lymphoma Grade 3: Review and Updates

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Abstract

Follicular lymphoma (FL), Grade 3, is recognized as a distinct entity in the World Health Organization classification of lymphoma. It is further classified into Grade 3a and Grade 3b depending on the Bernard cell counting system and percentage of centroblasts. Grade 3 has molecular and genetic characteristics that distinguish it from other grades of FL. There is confusion and misunderstanding about the natural history and clinical course of Grade 3a and 3b because some studies indicate them as having indolent behavior and others describe more aggressive biology. The purpose of this article is to understand the concept of Grade 3 FL, especially the fundamental differences between Grade 3a and Grade 3b FL. Grade 3 FL is still an evolving subclass in FL and the practicing physician should understand the aggressive nature of Grade 3b, which typically requires timely attention, compared with Grade 3a. Grade 3a FL has more indolent characteristics but can possibly progress to Grade 3b and/or transform to diffuse large B-cell lymphoma at a future time. Nevertheless, large prospective studies are missing for an optimal evidence-based management approach for patients with Grade 3 FL at this time.

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Introduction

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin lymphoma (NHL). It is defined as a lymphoma of follicle center B cells, and virtually always demonstrates a growth pattern that is partially follicular and accounts for 22% of newly diagnosed NHL.[1] The classification of FL has evolved through major changes over the past century. These were formally recognized as centroblastic/centrocytic follicular or follicular centroblastic according to the Kiel classification[2-4] and follicular small cleaved, mixed, or large cell according to the International Working Formulation (IWF) classification. The Revised European American lymphoma (REAL) classification[5] and the most recent World Health Organization (WHO) classification[6] proposes the term, follicle center cell lymphoma, follicular Grade 1, 2, 3a, and 3b. Grade 3 (largely follicular large cell according to the IWF) is discriminated from Grades 1 and 2 (predominantly follicular small cleaved cell and mixed small and large cell according to the IWF).

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The Bernard cell counting method is used by the WHO classification schema to "grade" FL. Grade 1 is defined when 0 to 5 centroblasts per high-power field (HPF) are counted; Grade 2 when 6 to 15 centroblasts per HPF are counted; and > 15 centroblasts per HPF is accounted as Grade 3, which is again subdivided into Grade 3a when centrocytes are present and Grade 3b when solid sheets of centroblasts are present.[7]

The purpose of this article is to understand the concept of Grade 3 FL, especially the fundamental differences between Grade 3a and Grade 3b FL.

Pathology and Biology

Follicular lymphoma is a heterogeneous clinicopathologic entity that includes tumors derived from germinal center B cells, centrocytes (small cleaved follicular center cells), and centroblasts (large noncleaved follicular center cells).[8] The germinal center ancestry of these cells is principally supported by the identification of somatic mutations in the variable region of the immunoglobulin (Ig) genes (IgVH), which serve as a marker of germinal center transit.[9] The cells of FL express surface Igs, IgM > IgD > IgG > IgA, B-cell–associated antigens (CD19, CD20, CD22, CD79a, and CD79b), and CD10 positivity or negativity.[2]

Follicular lymphoma generally expresses CD10, B-cell lymphoma 2 (bcl-2) and bcl-6. CD10 is expressed more commonly among FL Grade 1 and 2 (> 90%) compared with FL Grade 3.[10-13] Moreover,

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CD10 positivity was observed in 91% of cases of FL Grade 1 and 2, 48% in Grade 3a, and 57% in Grade 3b. Multiple myeloma oncogene-1 (MUM1) antigen is expressed on late stage germinal center B cells and postgerminal center B cells. It is expressed in 50% to 75% of diffuse large B-cell lymphoma (DLBCL). The incidence of MUM1 in FL has been reported to be more common in Grade 3 (especially Grade 3b) than Grade 1 and 2.[14,15] The t(14;18) is present in 70% to 95% of FL involving the rearrangement of the bcl-2 gene.[16-18] Increased expression of bcl-2 is more frequently seen in FL Grades 1 and 2 than in Grade 3.[19] Bcl-2 protein was expressed in only 48% of lymphomas classified as Grade 3a and 57% of Grade 3b. Furthermore bcl-6 rearrangements are frequently encountered in DLBCL/FL Grade 3b, but again, they are rare in FL Grades 1 and 2.[13,20]

Ki-67 staining was reported to be greater in Grade 3 compared with Grades 1 and 2.[21,22] Other groups also demonstrated greater Ki-67 staining in large-cell FL and Grade 3 FL compared with other FLs.[23,24] An interesting phenomenon is the decreased incidence of MYC rearrangement and distribution of double hit or triple hit in all categories of FL (13%-22%).[25-30]

There are conflicting results regarding the biological differences between FL Grade 3a and 3b. Studies[20,24] have reported that the biopsies of FL Grade 3b sometimes had a DLBCL component and were significantly less likely to express CD10 and more likely to express cytoplasmic Igs and to differentiate into a plasmocytoid variant. FL Grade 3b is also less likely to harbor the t(14;18) but more likely to display aberrations in chromosome band 3q27 when a coexisting diffuse large B-cell component existed. FL Grade 3b will also more likely express tumor suppressor gene p53 when a diffuse large B-cell component is present.[31] In Table 1 the basic differences between FL Grades 3a, 3b, and DLBCL are summarized.[32]

Clinical Presentation

Follicular lymphoma occurs most commonly in middle-aged and elderly patients,[33,34] although it has been reported that FL Grades 3a and 3b are more common in the older population, with a low male:female ratio (0.9 vs. 1.8).[35]

Clinical presentation and behavior of FL differs according to the histological grade. It presents as advanced disease in 80% to 85% of FL Grade 1; 70% to 75% in Grade 2; and 65% to 70% of Grade 3. Systemic symptoms are observed 30% of Grade 3 FL compared with 20% in Grade 1 and 2 FL.[2]

Prognostic Factors

The Follicular Lymphoma International Prognostic Index (FLIPI) is a prognostic scoring system based on age, Ann Arbor stage, number of nodal sites involved, hemoglobin levels, and serum lactate dehydrogenase levels.[36] The FLIPI was developed based on a large set of retrospective data from patients with FL, and established 3 distinct prognostic groups with 5-year survival outcomes ranging from 52.5% to 91% (before the use of rituximab therapy).[36] In the National Lympho Care study, which analyzed the treatment options and outcomes of 2728 patients with newly diagnosed FL, use of the FLIPI allowed categorization of patients into 3 distinct prognostic groups.[37] In a more recent study conducted by the International Follicular Lymphoma Prognostic Factor Project, a prognostic model (FLIPI-2) was developed based on prospective collection of data from patients with newly diagnosed FL treated with rituximab-era–containing chemotherapy regimens.[38] The final model included age, hemoglobin levels, longest diameter of largest involved lymph node, β-2 microglobulin levels, and bone marrow involvement. FLIPI-2 is highly predictive of treatment outcomes and allows separation of patients into 3 distinct risk groups with 3-year progression-free survival (PFS) rates ranging from 51.5% to 91% and overall survival (OS) rates ranging from 82% to 99%; the FLIPI-2 also allowed definition of distinct risk groups among the subgroup of patients treated with rituximab-containing regimens, with a PFS rate ranging from 57% to 89%.[38] Thus, FLIPI-2 might be useful for assessing prognosis in patients receiving active therapy with rituximab-based treatments. The FLIPI and FLIPI-2 allow prediction for prognosis, but these index scores have not yet been established as a means of selecting treatment options.

Follicular lymphoma tumors are graded from 1 to 3, and this grade has some prognostic utility. Differences in molecular genetics and clinical behavior suggest that FL Grade 3a is an indolent disease and 3b is an aggressive disease.[8,39] Although the follicular architecture is intact, the clinical presentation, behavior, and outcome with treatment in many patients with Grade 3b FL more closely

Table 1 Major Diagnostic Features of FL Grade 1 to 3a, FL Grade 3b, and Diffuse Large B-Cell Lymphoma

Characteristics	FL (1-3a)	FL (3b)	DLBCL
IHC	CD10+/bcl-6+/MUM1/IRF4-	CD10±/bcl-6+/MUM1/IRF4+	CD10±/bcl-6±/MUM1/IRF4±
Morphology	Follicular pattern	Common diffuse component	Diffuse architecture with large cells
Age	Mainly in adults	Also present in children	Also present in children
Genetics	• Mainly t(14;18) positive • Commonly bcl-6 transl neg • Bcl-6 ABR breakpoint region • IGH Sγ transl common • Common gains of chr 7	• Frequently t(14;18) neg • Frequently bcl-6 transl neg • Bcl-6 ABR breakpoint region - ?transl • Sometimes no gain of chr 7	• Commonly t(14;18) neg • Commonly 3q27/bcl-6 transl positive • Bcl-6 MBR breakpoint region • IGH Sμ transl common • Rare gains of chr 7
Prognosis	Favorable prognosis (except 3a)	Generally bad prognosis	Generally bad prognosis

Simplified scheme indicating frequent/predominant patterns. '+' Indicates positivity, '−' indicates negativity, and '±' indicates positivity or negativity.
Abbreviations: ABR = alternative breakpoint region; chr = chromosome; FL = follicular lymphoma; IGH = immunoglobulin heavy chain; IHC = immunohistochemistry; MBR = major breakpoint region; MUM1 = multiple myeloma oncogene-1; neg = negative; transl = translocation.
Adapted from Salaverria and Siebert.[32]