The Expanding Spectrum of Follicular Lymphoma

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KEYWORDS

• Follicular lymphoma • Non-Hodgkin lymphoma • Hematopathology

Key points

- Follicular lymphoma (FL) is a common B-cell lymphoma of germinal center origin, with classically associated clinical, histomorphologic, and genetic features.
- Grading of classic, nodal FL has undergone substantial shifts, and it is important to differentiate grades 1 to 2 disease from grades 3A and 3B.
- FL variants include those associated with age (pediatric FL) and anatomic site (primary intestinal FL and primary cutaneous follicle center cell lymphoma) and are associated with generally good prognosis.

ABSTRACT

Follicular lymphoma is a far more heterogeneous entity than originally appreciated. Clinical and biological variants are increasingly more granularly defined, expanding the spectrum of disease. Some variants associate with age, whereas others with anatomic site. Identification of these biologically distinct diseases has real prognostic and predictive value for patients today and likely will be more relevant in the future. Understanding of follicular lymphoma precursors has also made their identification both scientifically and clinically relevant. This review summarizes the features and understanding of follicular lymphoma, variants, and precursor lesions.

OVERVIEW

Classic nodal FL is commonly encountered in diagnostic practice and most often associated with typical morphologic and cytogenetic features (**Table 1**). Histologically, the nodular pattern is readily identified from low power by light microscopy, in part recapitulating expected follicular architecture (**Fig. 1**A, B). In most cases, the tumor cells express markers of germinal center B cells (CD10 and the master regulator of the germinal center reaction, BCL6) and harbor the t(14;18)(q32;q21) rearrangement. The translocation is associated with overexpression of BCL2, in distinct contrast to the germinal centers of reactive follicular hyperplasia (see **Fig. 1**C, D). Also in contrast to their reactive counterparts, low-grade FL typically shows low Ki-67 expression, a helpful diagnostic immunohistochemical feature (see **Fig. 1**E, F). Bone marrow involvement at presentation is identified in approximately 40% of patients.[1] The infiltrate is often composed of nodules adjacent to the trabecular bone, but paratrabecular localization is not specific for FL and similar patterns are seen in other morphologically low-grade non-Hodgkin lymphomas, including lymphoplasmacytic and mantle cell lymphoma.

Histologic grade can be assigned to FL based on the average number of large cells (centroblasts) per malignant follicle based on the 3-grade scheme originally adopted by the World Health Organization.[2,3] Grading has undergone revision because no clear meaningful prognostic significance was appreciated between grades 1 and 2 FL. Thus, distinguishing between grades 1 and 2 is not necessary in practice.[4–7] The division of grade 3 disease into grades 3A and 3B based on

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Table 1
Classic diagnostic features of nodal follicular lymphoma

Morphology	Back-to-back follicles lacking polarization
Grading	Grade 1–2: ≤15 centroblasts/high-power field Grade 3A: >15 centroblasts/high-power field; centrocytes present in the background Grade 3B: >15 centroblasts/high-power field; sheets of centroblasts without centrocytes present
Genetics	t(14;18)(q32;q21); *BCL2;* IGH rearrangement in majority of grades 1–2, decreasing in frequency in grade 3A and negative in grade 3B
Immunophenotype	Positive: CD19, CD20, CD10, BCL6, BCL2 Follicular dendritic cell meshworks: CD21, CD23, CD35

the presence or absence of centrocytes, respectively, seems clinically and biologically relevant (**Fig. 2**).[8] Grade 3B FL infrequently harbors the t(14;18) and typically lacks expression of CD10 or BCL2. Expression of other germinal center makers, however, including LMO2 and HGAL GCET2, seem preserved in grade 3FL and may be useful for disease classification.[9,10] In contrast, expression of the postgerminal center transcription factor, IRF4/MUM1, is common in grade 3B FL.[8] In many respects, the biology of grade 3B FL more closely aligns with that of diffuse large B-cell lymphoma (DLBCL) rather than lower grades of FL. A large retrospective study showed that grades 1, 2, and 3A followed a similar and indolent clinical course, whereas patients with grade 3B FL had a lower overall survival.[11] Anthracycline-containing therapies seem to improve overall survival of patients with grade 3B FL to that associated with grades 1 and 2 FL.[11]

A majority of low-grade FL are indolent, but approximately 20% to 30% follow an aggressive clinical course with transformation to DLBCL and refractoriness to therapy.[12] (See Montgomery, Mathews: Transformation in low-grade B-cell neoplasms, in this issue). To date, there is no robust and well-established biomarker to identify this subset. Prognostic parameters, however, including age, lactate dehydrogenase, β_2-microglobulin, and extent of disease are commonly used and incorporated into clinical scoring systems.[13] Apart from grade, histopathologic markers have been investigated, but they have not been uniformly adopted. Ki-67 expression by immunohistochemistry seems to correlate with histologic grade. Nonetheless, there are conflicting published data as to the independent prognostic implications of Ki-67 expression.[11,14] Markers characterizing the tumor microenviroment, including expression of PD1 and CD14, are also being studied and show promise in better predicting disease course.[15,16] (See Mina Xu: Lymphoma microenvironment and immunotherapy, in this issue). Genetic and molecular factors that relate to FL development have also been the focus of recent study. Mutations in *MLL2*, *EZH2*, and *IRF4* and deletions of EPHA7, for example, are frequent in the genetic landscape of FL, but further study is necessary to assess prognostic and predictive significance.[17–19]

In patients with FL, diffuse areas composed of large cells are diagnostic of transformation/progression to DLBCL and should be reported as such. Diffuse areas of small, mature-appearing lymphocytes, however, are not infrequently identified in low-grade cases of FL and do not represent transformation of disease. The degree of "follicularity" can be assessed by immunostains highlighting the follicular dendritic cell meshworks (CD21 or CD23) and the pattern reported as follicular (<25% diffuse), follicular and diffuse (25%–75% diffuse), or diffuse (<25% follicular). The diffuse pattern alone (ie, in the absence of large cell morphology) does not inherently have an impact on prognosis. As discussed later, however, unique biological subtypes may be associated more frequently with variant histologic appearances, including decreased follicularity.

FOLLICULAR LYMPHOMA VARIANTS

Although a majority of nodal FLs follow the clinical and biological paradigm (discussed previously), variations in clinical presentation, morphology, immunophenotype, and molecular underpinnings have been documented (**Table 2**). Appropriate identification and classification of these FL variants is clinically important, because they often have significant prognostic implications. Some variants associate with age, whereas others, somewhat uniquely, with anatomic location. In contrast to the expected clinical behavior imparted by histologic grade in classic FL, many of the FL variants are indolent, despite appearing histologically aggressive.