

Chapter 57

Follicular Lymphoma

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Definition

Follicular lymphoma (FL) is characterized by a clonal proliferation of mature B cells with phenotype and genotype of germinal center (GC) B cells composed of varying proportions of centrocytes and centroblasts, which usually has at least a partial follicular pattern. FL harbors the t(14;18) *IGH::BCL2* translocation leading to the overexpression of *BCL2* in up to 90% of cases. Diffuse areas of any size, composed of predominantly centroblasts, are evidence of progression to diffuse large B-cell lymphoma (DLBCL). Two early lesions closely related to conventional FL are recognized as variants, namely, in situ follicular neoplasia (ISFN) and duodenal-type follicular lymphoma (DTFL). Additionally, alternative forms of FL without *BCL2* rearrangements (*BCL2*-R) are recognized as distinct entities, including the new provisional entity of *BCL2*-R-negative CD23⁺ follicle center lymphoma (*BCL2*R-, CD23⁺ FCL), pediatric-type follicular lymphoma (PTFL), testicular follicular lymphoma (TFL), primary cutaneous follicle center lymphoma (PCFL), and large B-cell lymphoma with *IRF4* rearrangement (LBCL-*IRF4*),¹ and are classified separately from conventional FL.²

Synonyms

None.

Epidemiology

FL is the second most common lymphoma worldwide (after DLBCL) accounting for 20% of all non-Hodgkin lymphomas.³ Conventional FL predominantly affects adults with a median age of 60 years with most studies reporting no gender predilection and occurs very rarely in patients <18 years.³ It is more frequent in developed countries (25.5%) compared with developing countries (15.3%). In the United States, FL constitutes almost 40% of non-Hodgkin lymphoma and shows the highest incidence rate at 3.5 per 100,000. Furthermore, FL is most frequent in white populations followed by African and Asian/Pacific populations.^{3,4} The risk of FL

increases in patients with a family history of non-Hodgkin lymphoma, obesity, and Sjögren syndrome. Among environmental factors, pesticide exposure in agriculture (malathion and dichlorodiphenyltrichloroethane), living in industrial areas, smoking especially in females, professional spray painters, and hepatitis C virus infection increase the risk of FL.³

General Clinical Features

Sites of involvement

Most patients with FL have widespread disease at diagnosis (stage III or IV) including peripheral and central (abdominal, retroperitoneal, and mediastinal) lymphadenopathy. The bone marrow is involved in more than 40% to 50% of cases.⁵ The majority of patients probably have circulating neoplastic cells, and a small proportion are frankly leukemic. Despite widespread disease, patients are usually asymptomatic and B symptoms such as fever and weight loss are uncommon. A non-nodal presentation is less frequent and might involve the spleen, tonsils, skin, testis, or gastrointestinal tract. Notably, primary FL arising in the small intestine (particularly duodenum) is considered an early, localized FL lesion referred to as DTFL (see following discussion). Extranodal involvement of FL can have the same morphological and genetic characteristics as nodal FL. Alternative FL forms, especially those lacking *BCL2*-R such as *BCL2*R- CD23⁺ FCL, PCFL, PTFL, TFL, and LBCL-*IRF4*, should be distinguished from conventional FL and will be discussed in Chapters 58-62, respectively.

Clinical evaluation and staging

FL diagnosis is best made on an excisional lymph node biopsy, which provides the best opportunity to assess FL grade and growth pattern and also excludes possible areas of DLBCL transformation. The staging procedures for FL include physical examination, blood investigations (complete blood count, renal function and liver function tests, lactate dehydrogenase, and β 2-microglobulin), whole body computed tomography (CT) scan, and fluorodeoxyglucose positron emission

tomography (FDG-PET). FDG-PET is more sensitive than CT scan (especially at detecting extranodal FL or for up-staging early-stage patients to advanced-stage disease),⁶⁻⁸ and therefore, it is now the gold-standard imaging investigation at initial staging.⁹ It might also help guide the biopsy site in lesions with high glucose uptake (high standard uptake value) to rule out potential histologic transformation. The extent of the disease is then classified according to the Lugano classification. Assessment of bone marrow (BM) involvement with a BM biopsy is not necessary for staging but is recommended if the results modify patient management.

Morphology

Cytology

FL is composed of a mixture of centrocytes and centroblasts, which typically exhibit a follicular growth pattern (Figure 57.1). In most cases, centrocytes appear relatively small and more monomorphic than those in normal follicles and the few centroblasts stand out sharply from the monotonous background of centrocytes. The nuclei of centrocytes are usually less than twice the size of small lymphocytes but may be as large as nuclei of histiocytes or centroblasts. The nuclei of

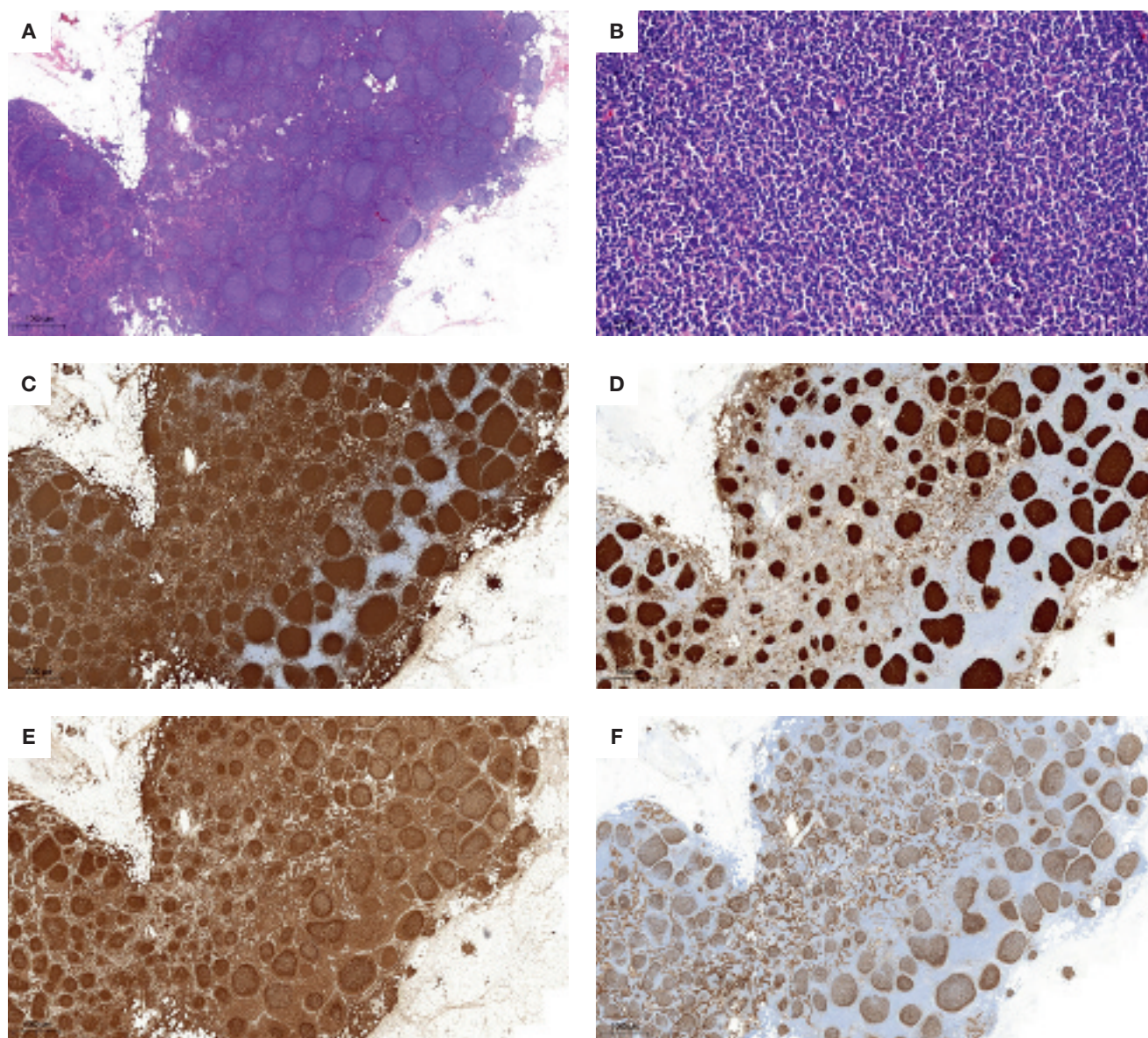


FIGURE 57.1 Lymph node with follicular lymphoma grade 1 to 2. **A:** The normal architecture of the lymph node is effaced by a neoplasia with follicular growth pattern. The neoplastic follicles are relatively uniform and closely packed without mantle zone. Focally there is extension into the extranodal adipose tissue. **B:** Most follicles are composed of centrocytes. **C-E:** Neoplastic cells strongly express CD20 (**C**), CD10 (**D**), and BCL2 (**E**). **F:** Tumor follicles are sustained by expanded CD21⁺ follicular dendritic cell meshworks.

centrocytes often are irregular or angulated with pale and evenly dispersed chromatin giving the nucleus a gray-blue appearance. They are surrounded by scant pale cytoplasm that is usually not visible on the hematoxylin and eosin (H&E)- or Giemsa-stained sections. Large centrocytes with dispersed chromatin and inconspicuous nucleoli may predominate. The nuclei of centroblasts are usually three to four times the size of small lymphocytes, similar to or larger than the nuclei of histiocytes. The nuclei are round or oval but may be irregular, indented, or even split. The nucleus is vesicular with a clear center and some peripheral chromatin condensation. One to three basophilic nucleoli are often attached to the nuclear membrane. The proportion of centroblasts may vary among follicles. Mitotic activity is usually low, and a starry-sky pattern with tingible body macrophages is rare. Rare cases of FL are composed of blastoid-appearing cells, with dispersed chromatin resembling lymphoblasts. This morphology is associated with a more aggressive clinical course.

Cytological variant of conventional FL

Cytological variants of FL are well recognized. In about 10% of conventional FL, marginal zone differentiation or monocytoid appearing B cells are observed in the

periphery of the follicles.¹⁰ Plasmacytic differentiation, although uncommon, might be observed (Figure 57.2).¹⁰ The plasma cells are believed to be part of the neoplastic population, carry the t(14;18) translocation, and are distributed predominantly in the interfollicular area. The morphology of the plasma cells ranges from small mature cells to somewhat atypical forms. Rarely, the neoplastic cells may have a signet ring cell appearance with clear cytoplasmic vacuoles and others may contain Dutcher bodies. Other rare cases may contain intrafollicular amorphous deposits that stain strongly for CD10 and CD20.¹¹ FL cases with hyaline-vascular Castleman-like feature have been also reported.¹² Finally, few FL cases can contain some intrafollicular giant or multinucleated cells resembling Hodgkin-Reed-Sternberg cells.

Grading

FL follicles are composed of various proportions of centrocytes and centroblasts. FL grading is determined by the number of centroblasts (CBs) per high-power field (HPF) (10-20 HPF in randomly selected follicles 40×): grade 1 $\leq$ 5CB/HPF, grade 2 = 5 to 15 CB/HPF, and grade 3 or high grade $\geq$ 15 CB/HPF. Grade 3 is subdivided into grades 3A and 3B (Figures 57.3 and 57.4);

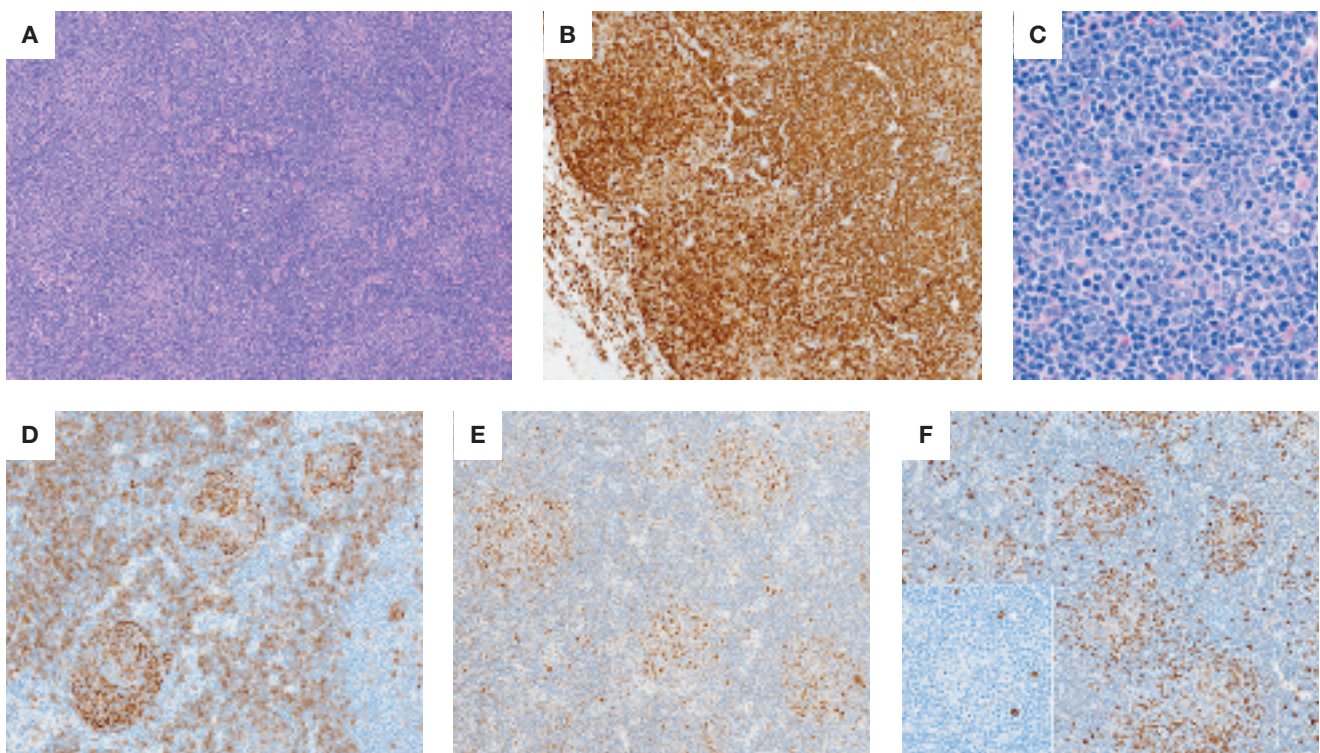


FIGURE 57.2 Follicular lymphoma (FL) with plasma cell differentiation. **A:** The lymph node architecture is effaced by a follicular neoplasm. **B:** Neoplastic cells are BCL2 positive. **C:** Giemsa stain shows neoplastic cells with plasmacytic differentiation. The cells have small nucleoli and scant basophilic cytoplasm. **D:** CD23 shows follicular dendritic cell meshwork and a variable expression on FL cells in interfollicular area. **E:** Neoplastic cells are BCL6 positive. **F:** The neoplastic cells are kappa positive (F) and lambda negative (inset).

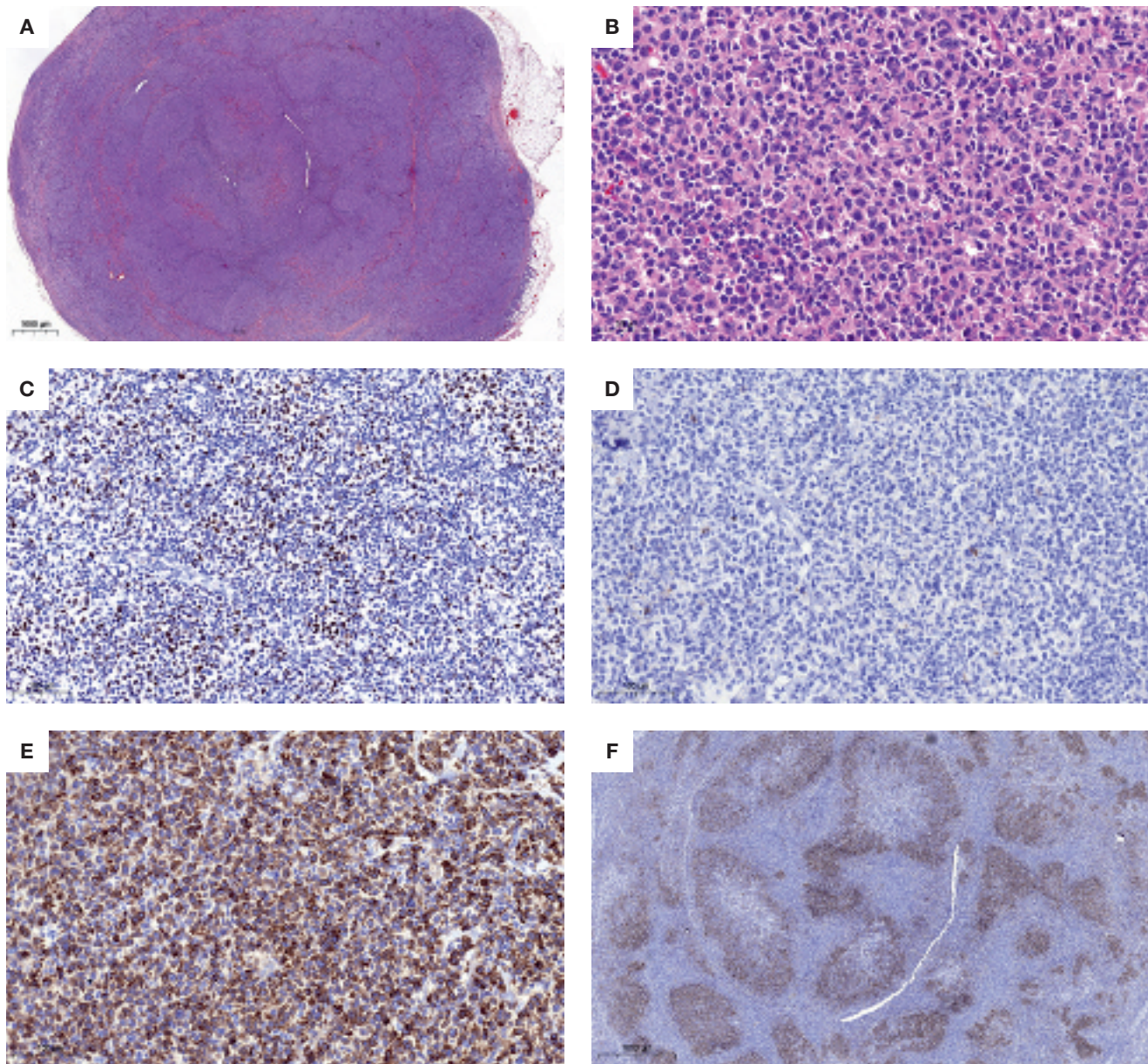


FIGURE 57.3 Lymph node with follicular lymphoma grade 3A. **A:** The lymph node architecture is completely effaced by a follicular proliferation. **B:** The neoplastic follicles are composed of centrocytes and numerous centroblasts (>15 CB/HPF). **C** and **D:** Neoplastic cells are BCL6 positive (**C**) and CD10 negative (**D**). **E:** Neoplastic cells strongly express BCL2. **F:** CD21 staining shows follicular dendritic cell meshworks.

the latter is assigned to FL cases in which neoplastic follicles are essentially composed of sheets of centroblasts and are usually treated as DLBCL.⁵ Moreover, because grades 1 and 2 comprise a morphologic continuum and are both clinically indolent, the designation grade 1 to 2 (low-grade FL) introduced in the 2008 World Health Organization classification⁵ is still recommended (Figure 57.1). However, FL grading based on strict counting methods of centroblasts and centrocytes lacks reproducibility in some cases,¹³ and its clinical impact, especially between grade 1 to 2 and 3A, appears to be

less significant in the era of rituximab.^{14,15} Some grade 3 FL cases, composed of neoplastic cells that are not classic centroblasts but rather small-sized blasts or large cleaved cells, are still considered as grade 3.¹ In these difficult cases, the demonstration of *BCL2*-R and CD10 expression that both favor grade 3A is useful and recommended. Finally, despite the biological relationship between grade 1 to 2 and 3A, and the difficulties in FL grading,¹ histologic grading is still maintained, in part to allow for investigation of response of new agents and pursue clinical investigation.^{1,2} Notably, new

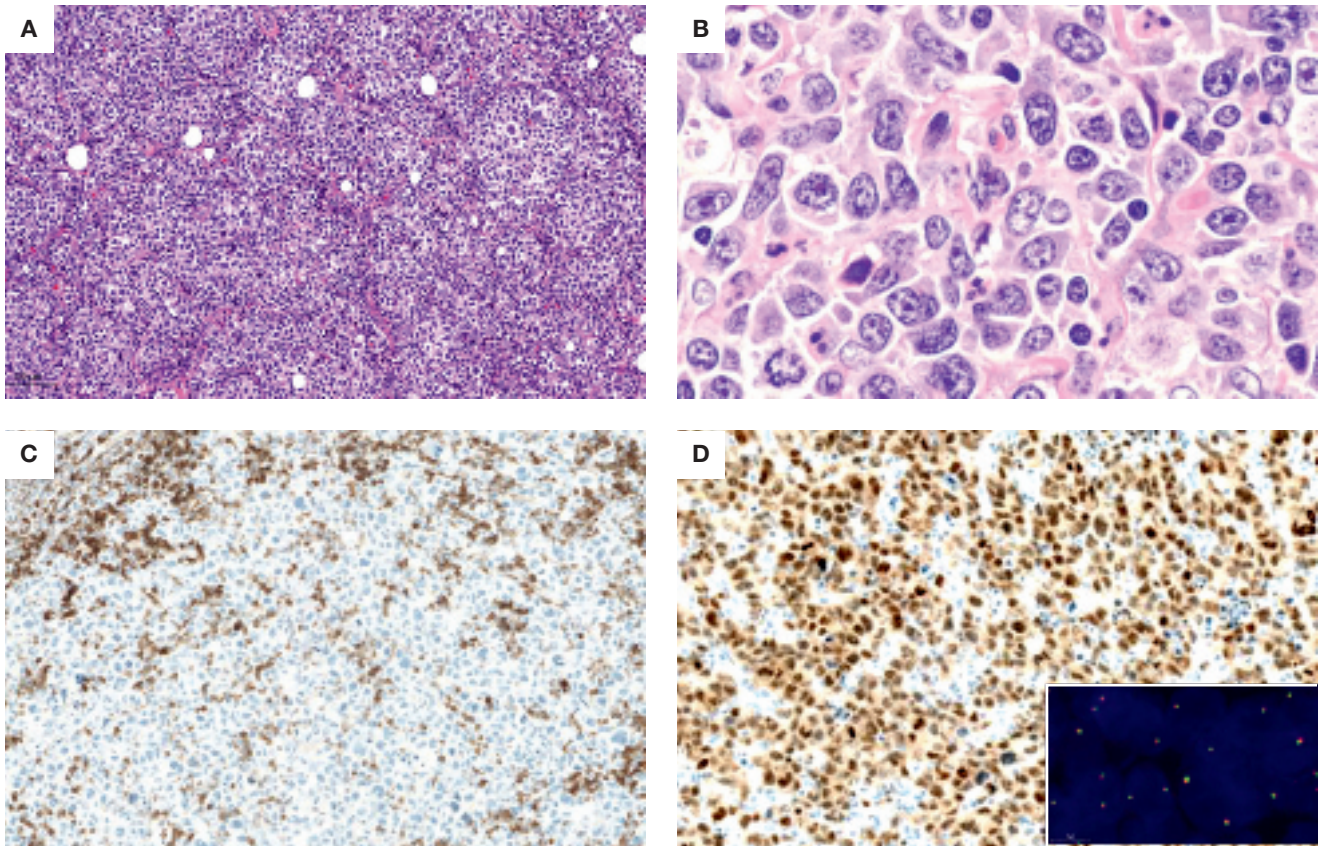


FIGURE 57.4 Lymph node with follicular lymphoma grade 3B. **A:** The lymph node architecture is effaced by a follicular neoplasia with back-to-back follicles and absent mantle zone. **B:** Higher magnification demonstrates that the neoplastic follicles are composed of sheets of centroblasts with no evidence of centrocytes. **C:** The neoplastic cells are negative for BCL2. **D:** IRF4/MUM1 is strong and homogeneously expressed in the tumor cells (inset: fluorescence in situ hybridization using *IRF4* break apart probes is negative).

genetic studies have shown that the separation between FL grade 1/2 and 3A matters and has clinical impact.¹⁶

Pattern

FL is characterized by an effacement of normal lymph node architecture by closely packed neoplastic follicles sustained by a follicular dendritic cell (FDC) network. However, sometimes more and less extended diffuse areas can be observed. Diagnostic reports traditionally identify the growth pattern, with designations of mainly follicular pattern (at least 75%), FL with follicular and diffuse pattern (25%-75%), predominantly diffuse (<25%), and totally diffuse (no follicles). Diffuse FL diagnosis should be made with caution after excluding other lymphomas, especially DLBCL in case of predominant large B-cell proliferation (Figure 57.5). Moreover, the new provisional entity *BCL2R-CD23⁺* FCL (see Chapter 58) often has a diffuse growth pattern and should be distinguished from conventional FL.^{1,2} Neoplastic follicles may vary in size from a primary follicle to much larger than reactive follicles. They usually are round and monotonous with loss of

follicle polarization, absence of body macrophages, and attenuated mantle zones. Sometimes follicles may be irregular and serpiginous, mimicking florid reactive hyperplastic follicles. Mantle zones are attenuated or absent.

Tumor microenvironment

In addition to FDC, neoplastic follicles contain numerous CD4⁺ follicular helper T cells (T_{FH}), some classic regulatory T cells (T_{REG}), and follicular regulatory T cells (T_{FR}).¹⁷ The interfollicular region usually shows a reduced normal T-cell zone with variable amounts of T_{REG}. CD8⁺ T cells frequently exhibiting an exhausted phenotype and some cytotoxic T cells that are usually observed at the follicle border.^{18,19} There are few plasma cells. Macrophages and stroma cells also contribute to FL's tumor microenvironment (TME) and are usually present in the interfollicular region.²⁰ FL may contain numerous blood vessels with high endothelial venules often infiltrated by neoplastic centrocytes. Subcapsular and medullary sinuses are typically obliterated but may be partially preserved in some cases. Sclerosis is

common and may present surrounding the follicle, in diffuse areas (especially when FL is in mesenteric and retroperitoneal regions) or less often in the follicle. Extrascapular extension is common and leads to the formation of fibrous bands in the extranodal tissue.

Immunophenotype

FL cells express the pan B-lymphocyte antigens (CD19, CD20, CD22, CD79a, PAX-5) and express IgM with or without IgD. Similar to normal GC cells, FL cells also express CD10 and BCL6, usually stronger in the neoplastic follicles than in interfollicular areas. However, a subset of FL, especially grade 3B, can be negative for CD10 and/or BCL6. In this context, other GC markers including GCET1, HGAL (GCET2), LMO2, and/or MEF2B should be performed to rule out other B-cell lymphomas diagnoses. They are negative for CD5 and CD43.

FL cells typically overexpress BCL2 as a result of the genetic hallmark of FL, t(14;18) *IGH::BCL2* translocation. Similar to CD10 staining, the frequency of BCL2 expression is higher in grade 1 to 2 (85%-90%) than in grade 3 (50%-70%) FL. However, some FL cases do not express BCL2 protein due to the absence of *BCL2-R*.²¹ In addition, some FL cases harboring t(14;18) may be falsely negative when stained with an anti-BCL2 antibody, due to mutations in the *BCL2* gene that alter the epitopes recognized by some monoclonal antibodies. In these “pseudonegative” cases, other anti-BCL2 antibodies (clones E17 or SP66) and/or fluorescence in situ hybridization for *BCL2-R* should be tested.²²

IRF4/MUM1 is typically not expressed except in some cases of high-grade FL, especially grade 3B (see later discussion). In the case of FL grade 3

expressing MUM1/IRF4, the International Consensus Classification (ICC) recommends evaluating *IRF4* alterations, especially in younger patients, to rule out the diagnosis of LBCL *IRF4-R* (discussed in Chapter 62).^{1,2} A nodular pattern is assessed by the presence of CD21, CD23, and/or CD35 positivity in the FDC meshwork but absent in cases with diffuse areas. Some FL neoplastic cells can also express CD21 or CD23. Most, but not all, grade 1-2 FL have a low Ki-67 proliferation index (<20%), but due to heterogeneity of distribution, it is still difficult to assess and alone, its clinical significance remains uncertain. Finally, Ki67 is not required for grading.

Genetics

Antigen receptor genes

The immunoglobulin (IG) heavy chain and light chain genes are clonally rearranged, and IG variable gene regions show extensive and ongoing somatic mutations. Similar to normal GC B cells, FL cells express activation-induced cytidine deaminase (AID) in >25% of FL, an essential requirement for somatic hypermutations (SHMs) and isotype switch.²³ About 40% to 50% of FL have undergone isotype switching and express IgG, and surprisingly, most IgM⁺ FLs show class-switch recombination (CSR) on the translocated allele and IGHC deletions on the expressed IGH allele.²⁴ Retention of IgM expression in FL cells could be advantageous for (pre)malignant cells, as it appears that IgM⁺ memory B cells have a greater propensity to reenter GC than class-switched memory B cells.

Although linear clonal evolution has been described, most FL cases follow a subclonal evolution from a common precursor cell, leading to multiple subclones

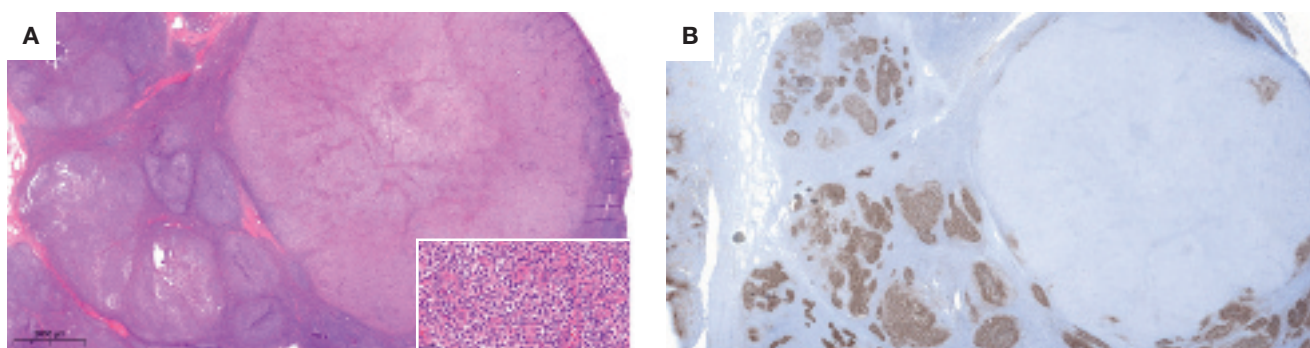


FIGURE 57.5 Lymph node infiltrated by follicular lymphoma (FL) with a component of diffuse large B-cell lymphoma (DLBCL). **A:** This lymph node shows two different areas. On the left side there is infiltration by neoplastic follicles without mantle zones. The infiltrate is composed of admixed centrocytes and centroblasts corresponding to FL grade 1-2. The second area on the right side shows a diffuse area composed of sheets of large cells consistent with DLBCL (inset: high magnification showing diffuse proliferation of large centrocytes and centroblasts). **B:** CD21 staining shows follicular dendritic cell meshworks in the follicular areas but not in the DLBCL.

already identified in the early stages of FL (early FL lesions, see later discussion) that provide the substrate for FL progression and transformation.²⁵

In addition, FL cells have a high incidence of N-glycosylation sites (Asn-X-Ser/Thr) introduced by SHM, mostly in the IG variable gene regions²⁶ that induce FL interactions with TME via surface structures (C-type lectins, dendritic cell–specific ICAM-grabbing nonintegrin, and mannose receptors) and that promote FL survival.

Cytogenetic abnormalities

FL with *BCL2* rearrangement

The translocation t(14;18)(q32;q21), or on rare occasions its variants t(2;18)(p12;q21) or t(18;22)(q21;q11), is the hallmark of conventional FL occurring in 85% to 90% of cases and leading to the overexpression of the antiapoptotic protein BCL2. *BCL2*-R is more often observed in low-grade than in high-grade FL. The t(14;18) can also be detected at very low levels (~1–100 cells per million B cells) in the peripheral blood (PB) of >70% healthy adults (referred as “FL-like cells”). The frequency of FL-like cells in PB increases with age and risk exposure (pesticides).²⁷ Although higher levels of circulating FL-like cells are associated with an increased risk of developing an overt FL, the vast majority of those healthy individuals will never develop FL,²⁸ indicating that the translocation alone is not sufficient for the development of FL and additional genetic alterations are needed for full transformation. In fact, the acquisition of t(14;18) allows FL-like cells to iteratively reenter GC and engage in multiple cycles of SHM and CSR, thereby increasing the risk of accumulation of genomic instability.

FL without *BCL2* rearrangement (*BCL2*-R negative)

BCL2-R-negative FL represents 10% to 15% of FL cases and constitutes a heterogeneous group of FL.^{21,29,30} Based on clinical presentation, *BCL2*-R-negative FL can be divided into three groups: (1) nodal presentation, (2) extranodal presentation including the PCFL, and (3) those affecting predominantly children and young adults such as PTFL, TFL, and LBCL *IRF4*-R. Of note, PCFL, PTFL, TFL, and LBCL *IRF4*-R are considered as distinct entities separate from conventional FL in the ICC 2022^{1,2} (see Chapters 59–62). Regarding nodal *BCL2*-R-negative FLs, genetic studies comparing *BCL2*-R negative and *BCL2*-R positive FLs have pointed out subtle differences in the developmental stages of the neoplastic B cells, the usage of divergent oncogenic pathways, and the composition of the microenvironment.³¹ Likewise,

genetic alterations frequently observed in *BCL2*-R+ FL have been reported in nodal *BCL2*-R-negative cases but at different frequencies, showing an enrichment of *STAT6* (57%) mutations followed by *CREBBP* (49%), *TNFRSF14* (39%), and *KMT2D* mutations²¹ as well as some variations in chromosomal alterations such as the most frequent *BCL6*-R and 1p36 deletion.

Based on their molecular profiles, three groups of nodal *BCL2*-R-negative FLs are identified: (1) *BCL2*-R-, CD23+ FCL, discussed in Chapter 58; (2) nodal *BCL2*-R-negative FL with *BCL6*-R (excluding FL3B, see later discussion); and (3) nodal *BCL2*-R-negative and *BCL6*-R-negative FLs. Nodal *BCL2*-R-negative FL with *BCL6*-R, grade 1–3A represents ~20% of *BCL2*-R-negative FLs. Patients with FL *BCL6*-R present with a more advanced clinical stage.³⁰ *BCL6*-R involving 3q27 with a variety of partners leads to anomalous upregulation and prevents the cell from progressing past the GC stage, thus facilitating neoplastic transformation. FL with *BCL6*-R grade 1 to 2 and 3A has a follicular pattern, usually conserves a GC phenotype, and shares similar genetic alterations with conventional FL *BCL2*-R+. However, it shows a more complex genetic profile and fewer *CREBBP* and *STAT6* mutations than other nodal *BCL2*-R-negative FLs.^{21,30} Nodal *BCL2*-R-negative and *BCL6*-R-negative FL grades 1 to 2 and 3A are characterized by few genetic alterations, noninguinal presentation with follicular growth pattern, and lack of both *STAT6* mutations and CD23 expression.²⁹ The differential diagnosis of nodal marginal zone lymphoma (MZL) can be challenging. However, these cases express at least one GC marker and lack typical mutations of nodal MZL.

Other genetic alterations

Copy-number alterations are found in most FLs and include chromosomal gains of 18, X, 1q, 2p, and 7, and less commonly gains of 17q, 6p, 8q, 12q as well as deletions of 6q and 1p and less frequently deletions of 10q and 9p.^{5,32} Genomic alterations in *TP53* or *CDKN2A* and *MYC* translocations are rare and have been reported to be associated with high-grade features and/or increased risk of transformation. However, the prognostic value of de novo *BCL2*-R positive FL with *MYC*-R is still controversial. Based on the limited data available, de novo *BCL2*-R/*MYC*-R positive FL with should not be considered as high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements.²

Recurrent mutations in epigenetic regulators and chromatin remodeling genes are the most frequent mutations in conventional FL.³³ Among them, mutations in chromatin-remodeling genes such as

KMT2D/MLL2, *CREBBP*, and *EP300* represent common drivers of conventional FL. *KMT2D/MLL2* is the most frequently observed in 90% of cases followed by *CREBBP* in 33% to 75% of cases. Additional epigenetic dysregulation comprises gain-of-function mutations of *EZH2* (25%), a histone methyltransferase catalyzing trimethylation of lysine on histone H3 (H3K24me3). Other less frequent epigenetic modifier mutations are seen in *ARID1A*, *MEF2B*, and *KMT2C* genes. *BCL2* mutations are common due to AID activity. *TNFRSF14* mutations or 1p36 deletion (including *TNFRSF14* gene) can be observed in FL, irrespective of t(14;18). *STAT6*, *CARD11*, *FOXO1*, *NOCTH1/2*, and *TNFAIP3* mutations are less frequently seen in FL with *BCL2*-R. However, as mentioned previously, these frequencies of genetic alterations differ in nodal *BCL2*-R-negative FL, showing enrichment of *STAT6* mutations followed by *CREBBP*, *TNFRSF14*, and *KMT2D* mutated genes. Besides clonal evolution over time, studies have also demonstrated significant spatial heterogeneity in mutation and genomic profiles in different disease sites in a given patient.^{34,35} This hampers the development of prognostic biomarkers based on tumor genetic architecture.

Follicular Lymphoma Grade 3B

FL grade 3B, accounting for ~5 to 10% of all FL cases,³⁶ is defined by the presence of solid sheets of centroblasts (>15 CB/HPF) with at least a partial follicular pattern (Figure 57.4). Coexistence with DLBCL is frequent. FL3B should also be distinguished from FL3A. As mentioned earlier, ICC recommends evaluating the status of *BCL2*-R and CD10 expression in FL grade 3 (absence of *BCL2*-R and the CD10 expression favor the diagnosis of FL3B).^{1,2} *BCL2*-R is less frequently observed (9%-50%) in FL3B, whereas *BCL6*-R is reported in up to 40% and *MYC*-R in 20% of cases. The tumor cells are often negative for CD10 (40%-100%) and *BCL6* (0%-50%) and have a lower expression of *BCL2* and increased p53 expression.^{21,37} Moreover, *IRF4/MUM1* has been variably reported (42%-100%). In addition, CD10⁻ MUM1/IRF4⁺ FL grade 3 lacking *BCL2*-R and *BCL6*-R may be associated with poorer prognosis.³⁶ As mentioned earlier, FL 3B should be tested for *IRF4* alterations to exclude LBCL *IRF4*-R diagnosis (see Chapter 62). Additional cytogenetic abnormalities such as gain of chromosome 7 or 3 and 6q deletion have been reported.³⁸ As in conventional FL, epigenetic mutations including *KMT2D/2C* and *CREBBP* are the most frequent in pure FL3B.³⁹ *TP53* and *MYD88* mutations may

also be observed.³⁹ Two gene expression profiling studies concluded that FL3B has a distinct signature closer to that of FL3A and different from DLBCL and FL grades 1 to 2,^{40,41} supporting the contention that FL3B belongs to the group of FL rather DLBCL. However, further studies are needed to clarify this issue.

Prognosis and Clinical Outcome

FL is usually a disseminated but indolent disease with a median overall survival (OS) of patients between 15 and 20 years. Its prognosis is related to disease extent at diagnosis and other disease and patient characteristics. The Follicular Lymphoma International Prognostic Index (FLIPI) distinguishes three groups of patients (approximately one-third each) with significant differences in OS.^{42,43} The FLIPI uses five independent adverse predictors: age >60 years, hemoglobin <12 g/dL, elevated serum lactate dehydrogenase, Ann Arbor stage III/IV (disseminated disease in the Lugano system), and >4 involved nodal areas. The presence of 0 to 1, 2, 3-5 of these factors defines low-risk, intermediate-risk, and high-risk disease, respectively. Other clinical prognostic indices, such as FLIPI-2 and PRIMA-PI, are not commonly used in daily practice.^{44,45} Except for grade 3B, histological grade has no significant impact on outcome in patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) regimens.^{1,2} For patients requiring treatment, the use of combined immunochemotherapy results in a 10-year OS of around 80%. Despite recent therapeutic progress and improved OS, progression occurs over time in most patients. Early progression within 24 months of treatment initiation (POD24), occurring in 15% to 20% of FL, has a poor prognosis, with a variable but significant proportion of those patients experiencing histological transformation.

Recently, the m7-FLIPI (integrating FLIPI with seven common gene mutations) and some gene expression signatures related to dark zone CBs have been identified as prognostic indices but remain investigational.^{33,46-48} The composition and spatial distribution of the FL microenvironment have shown a prognostic impact of distinct subpopulations (Treg, T_{HH}, cytotoxic T cells, and stromal cells) in numerous studies, but there is still a lack of consensus regarding biomarkers.⁴⁹⁻⁵¹

Histologic transformation of FL to high-grade lymphoma, occurring at a risk of 1% to 3% per year,^{52,53} might affect 5% to 12% of patients with FL within 5 years of follow-up.⁵² The most common histology is DLBCL (mainly GCB rather than ABC subtype, 80% vs. 20%)

and more rarely Burkitt lymphoma, lymphoblastic lymphoma, or Hodgkin disease.^{52,54} High FLIPI score and resistance to first-line therapy have been reported as risk factors for transformation.⁵ In addition, genetic factors including deletions and gains (del 1q, del 6q, +2, +3q, +5), loss of *B2M*, and alteration of *CDKN2A/B*, *MYC*, and *TP53*^{55,56} have been associated with the risk of transformation, but early detection of molecular alterations predicting transformation has not been so far successful.

EARLY LESIONS OF FOLLICULAR LYMPHOMA

In Situ Follicular Neoplasia

Definition

ISFN is an FL variant characterized by a monoclonal proliferation of B cells carrying t(14;18) translocation and partially or totally colonizing the GC of some follicles in lymphoid tissue. ISFN is biologically similar to the presence of t(14;18) found in PB of healthy individuals, referred as FL-like B cells.⁵

Synonyms

None.

Epidemiology

ISFN is an incidental finding reported in 2% to 3% of unselected reactive lymph nodes from middle-aged or older individuals. However, some ISFN can occur syn- or metachronously with confirmed FL, as well as with other B-cell lymphomas.

General Clinical Features

For patients with incidentally diagnosed ISFN and no other evidence of FL on clinical evaluation, the risk of subsequent FL is very low (5%). The number of follicles involved by ISFN cannot predict the subsequent risk of developing FL. High levels of FL-like B cells in PB are associated with an increased risk of subsequent FL.

Morphology

ISFN is generally not apparent in routine H&E-stained sections. The lymph node has a preserved nodal architecture and contains reactive follicles with well-defined GC and intact mantle zones (Figure 57.6). The affected

follicles are similar in size and shape to uninvolved follicles. ISFN is distinct from partial involvement by FL, in which only selected follicles within an lymph node may be involved. Moreover, ISFN can only be observed with subsequent immunohistochemistry, whereas partial involvement by FL can be suspected on H&E-stained sections with at least focal areas of architectural effacement. Partial involvement by FL is associated with lower-stage disease that can histologically progress to full FL in 53% of the cases versus 5% of ISFN.⁵⁷

Immunophenotype

BCL2 is strongly expressed by the tumor B cells (mostly cleaved centrocytes-like cells) confined to the GC. BCL2 staining in tumor cells shows a higher intensity than in adjacent T cells or mantle zones. BCL2+ tumor cells also show strong expression of CD10 and BCL6 (Figure 57.6).

Genetics

ISFN cells carry the t(14;18) *IGH::BCL2* and share genetic alterations similar to systemic FL but at lower frequencies,^{58,59} suggesting that ISFN is a very early step in FL lymphomagenesis. Mutations in *CREBBP*, *KMT2D*, *TNFRSF14*, and *EZH2*; deletions in 1p36; and acquisition of N-glycosylation sites have been reported in ISFN.^{58,59} Recently, the *CREBBP* mutation has been shown to be the most commonly observed precursor lesion and may distinguish patients developing FL from healthy adults with or without detected *BCL2*-R.⁶⁰ In cases where ISFN and overt FL are seen in the same patient, there are additional genetic alterations in the FL not detected in ISFN. Recently, branched clonal evolution, rather than a linear one between early FL lesions and systemic FL, has been reported, suggesting that ISFN and FL evolve from a common progenitor.⁶¹

Duodenal-Type Follicular Lymphoma

Definition

DTFL is another FL variant defined by distinctive clinical and biological features.⁵ The lesions are predominantly found in the second portion of the duodenum, presenting as multiple polyps, often as an incidental finding on endoscopy performed for other reasons. Most patients have localized disease (stage IE or IIE). Cases without the typical features of DTFL should be investigated for evidence of conventional FL involvement at other sites. It also must be differentiated from primary intestinal FL,

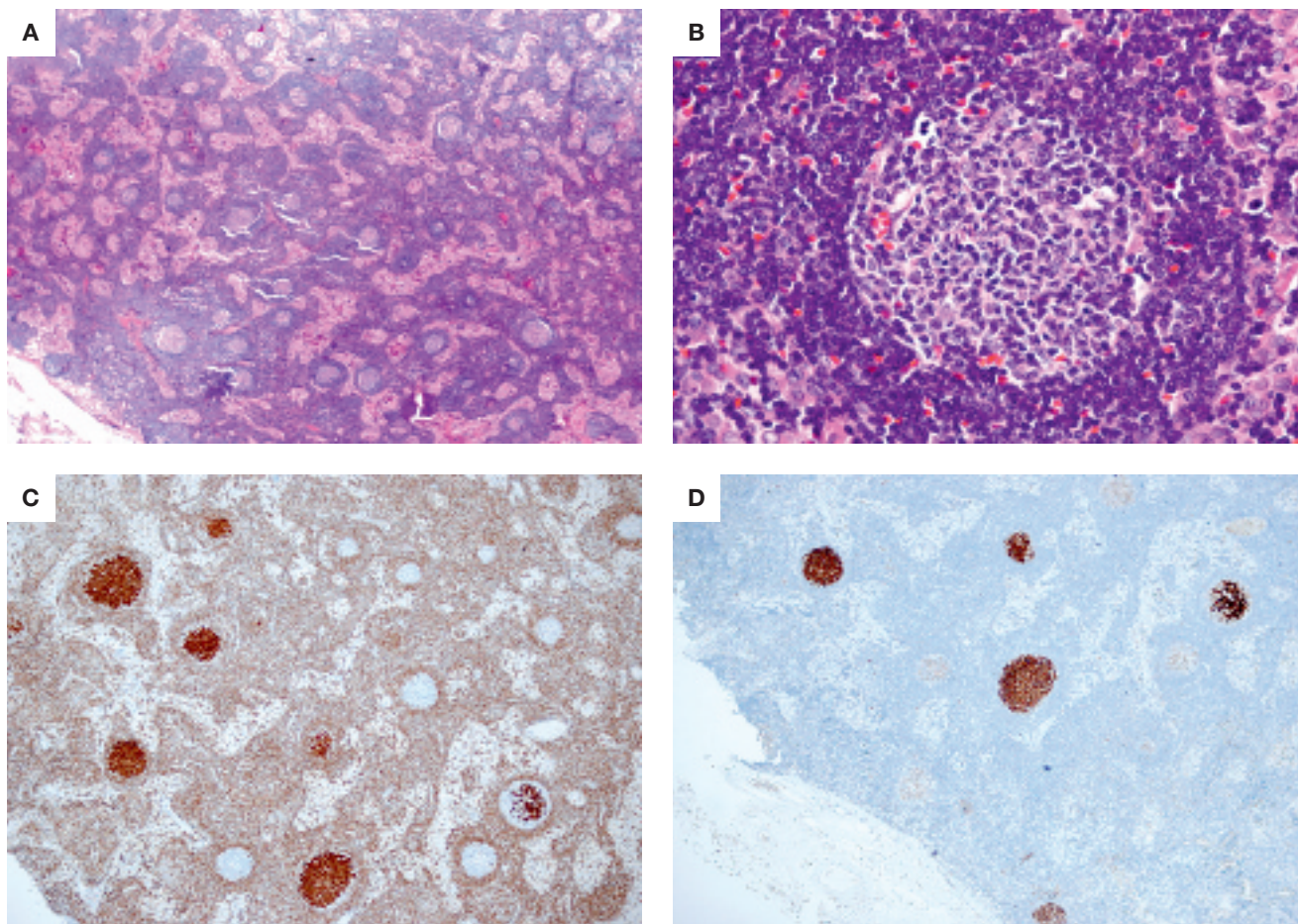


FIGURE 57.6 In situ follicular neoplasia. **A:** Lymph node biopsy shows preserved nodal architecture with reactive follicles and open sinuses. **B:** The follicle is small with a well-defined germinal center surrounded by an intact mantle zone. It contains mainly centrocytes. **C:** BCL2 stain highlights the few follicles, which are BCL2 positive. Note that the expression of BCL2 in the follicles is stronger than in reactive B and T cells. **D:** Neoplastic cells show increased expression of CD10 when compared with the residual normal germinal centers.

which often shows transmural infiltration with systemic spread and variation in cytological grade.

Synonyms

None.

General Clinical Features

DTFL has an indolent clinical course, often without therapy. Local recurrences can occur. There is a low progression to nodal disease. Clinical evaluation and staging are essential to exclude systemic FL secondarily involving the bowel, which follows a more aggressive course.

Epidemiology

DTFL accounts for 4% of all primary gastrointestinal lymphomas. The small intestine, especially duodenum, is most often involved, although stomach and

colorectum may be affected. Most patients are middle aged, with an equal male-to-female ratio in most series.

Morphology

DTFL is characterized by a neoplastic follicular proliferation localized to the mucosa/submucosa and composed of mostly centrocytes, corresponding to grades 1 to 2 in the grading system for nodal FL (Figure 57.7).

Immunophenotype

The DTFL immunophenotype is similar to that of nodal FL. The cells are positive for CD10, CD20, BCL6, and BCL2. There is also frequent expression of IgA and alpha4 beta7 integrin, which is a mucosal homing receptor. FDCs demonstrated by CD21 or CD23 expression are characteristically restricted to the periphery of the follicles.⁶² The proliferation rate is generally low.

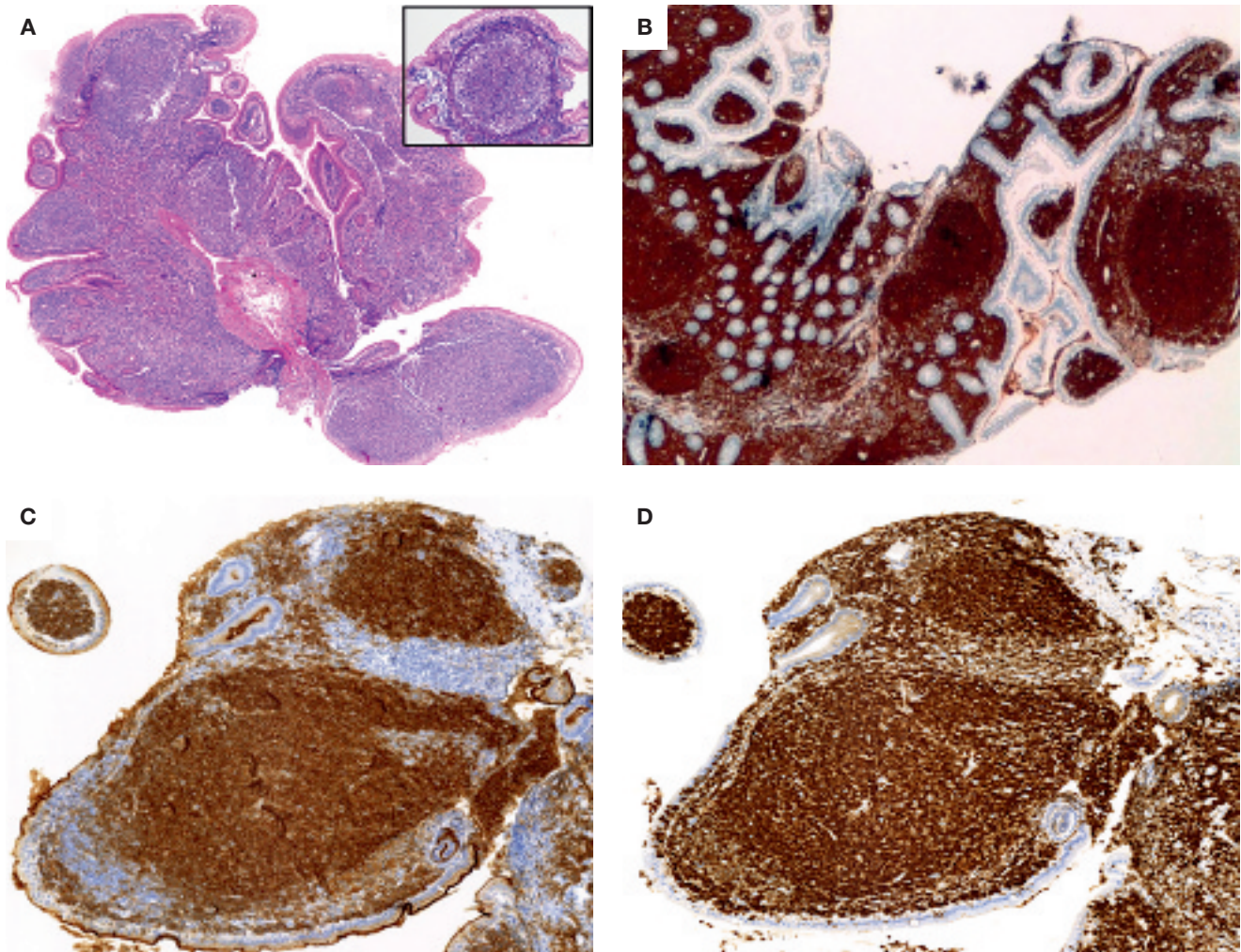


FIGURE 57.7 Duodenal-type follicular lymphoma. **A:** Duodenal polyp found incidentally in a patient undergoing screening endoscopy (inset: high magnification of atypical lymphoid follicle showing mostly centrocytes with lack of polarization). **B:** CD20 stain. **C:** Neoplastic cells express CD10. **D:** Neoplastic cells are BCL2 positive.

Genetics

Tumor cells carry the t(14;18) translocation and also mutations typically encountered in conventional FL such as *TNFRSF14* (or del 1p), *EZH2*, *KMT2D*, and *CREBBP*. The frequency of *KMT2D* mutations is lower than in conventional FL, as is its genetic complexity. DTFL is thought to derive from memory B cells and show evidence of SHM of the IGH gene. Restricted IGHV usage (VH4 and VH5) suggests similarities to mucosa-associated lymphoid tissue (MALT) lymphoma. Genomic expression profiling also suggest an overlap with MALT lymphoma, showing an enrichment for a chronic inflammation signature including overexpression of *MADCAM1* and *CCL20*, which recruits proinflammatory Th17⁺ cells.⁶³

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