Review

The broad landscape of follicular lymphoma: Part I

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Summary

Follicular lymphoma is a neoplasm derived from follicle center B cells, typically both centrocytes and centroblasts, in variable proportions according to the lymphoma grading. The pattern of growth may be entirely follicular, follicular and diffuse, and rarely completely diffuse. It represents the second most common non-Hodgkin lymphoma, after diffuse large B-cell lymphoma and is the most common low-grade mature B-cell lymphoma in western countries. In the majority of cases, follicular lymphoma is a nodal tumor, occurring in adults and frequently associated with the translocation t(14;18)(q32;q21)/IGH-BCL2. However, in recent years the spectrum of follicular lymphoma has expanded and small subsets of follicular lymphoma, which differ from common follicular lymphoma, have been identified and included in the current 2017 WHO classification. The aim of our review is to describe the broad spectrum of follicular lymphoma, pointing out that the identification of distinct clinicopathological variants of follicular lymphoma is relevant for patient outcomes and choice of treatment.

Key words: follicular lymphoma, B-cell, centrocyte, centroblast

Introduction

Follicular lymphoma (FL) is the most common low-grade mature B-cell lymphoma in western countries, representing 20% to 30% of all non-Hodgkin lymphomas [1]. It is defined as a neoplasm composed of germinal center (GC) B cells, recapitulating the cellular composition and architecture of normal lymphoid follicle [1]. It usually affects adults, with a median age in the 6th decade of life[1]. The updated 2017 World Health Organization (WHO) Classification includes critical news about FL [1]. In recent years, the histological and clinical spectrum of GC derived B-cell neoplasms has expanded, leading to the conclusion that FL represents a far more heterogeneous entity than originally appreciated. Some variants are associated with age, and others with anatomic site, morphological pattern and genetic features. Clinical and biological variants of FL exist, expanding the disease spectrum. Identification of biologically distinct variants has prognostic and predictive value for patients and will be likely more relevant in the future. In the present review we illustrate FL variants encountered in diagnostic practice. Surgical pathologists and hematopathologists should be aware of the broad FL landscape, in order
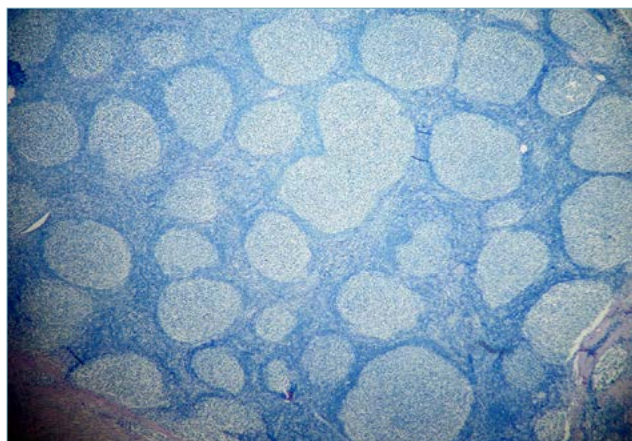
Figure 1. Lymph node. Follicular lymphoma. Giemsa, 40x magnification.

to avoid diagnostic pitfalls and obtain more accurate diagnosis.

Histopathology of common nodal FL and diagnostic criteria to differentiate FL from reactive follicular hyperplasia

FL is a mature B-cell lymphoma of germinal center origin, with strict morphologic criteria and specific immunophenotype. At microscopical examination, nodal architecture is effaced by closely packed follicles with a back-to-back distribution (Fig. 1). Sometimes follicles may be spaced out, irregular, serpiginous, coalescent or with regressive "Castleman-like" changes. Follicles are surrounded by a thin residual mantle zone or they can completely lack the mantle. Sometimes the follicle border is vague, not sharply defined. Neoplastic follicles show a cellular population composed by an admixture of centrocytes with a variable number of centroblasts; tingible body macrophages are usually rare and a starry sky appearance is commonly ab-

sent. Centrocytes are small cells with cleaved nuclei, inconspicuous nucleoli and scant cytoplasm. Centroblasts show vesicular chromatin with 1 to 3 small nucleoli located near the nuclear membrane. Unlike reactive GC (in the secondary phase of development) in which centrocytes and centroblasts are polarized in different zones, neoplastic follicles lack polarization in dark and light zones, as confirmed by Ki-67 immunostaining. FL is usually positive for CD10, BCL6 and BCL2 and the translocation t(14;18)/IGH-BCL2 commonly represents its hallmark [1]. CD10 and BCL6 can be down regulated in the interfollicular areas, showing a stronger staining in the follicles than in the interfollicular zones [1]. Many features are helpful to distinguish FL from reactive follicular hyperplasia (RFH), as briefly illustrated in Table I. However, these features are general diagnostic criteria, which need to be verified case by case, taking into account that exceptions always do exist.

How to easily apply the grading system and report pattern criteria in FL according to updated 2017 4th ed. WHO classification

The number of centroblasts within neoplastic follicles is the basis for FL grading. WHO classification adopts the grading system initially proposed by Risa Mann and Costant Berard in 1983 [2]. The number of centroblasts in FL varies from follicle to follicle and grading is perfomed by counting the number of centroblasts in 10 follicles, expressed per high-power microscopic field (HPF) [1]. Ten HPF have to be evaluated within different follicles and not be limited to follicles containing the large amount of centroblasts [1]. Grade 1-2 contain a predominance of centrocytes (grade 1: 0-5 centroblasts/HPF; grade 2: 6-15 centroblasts/HPF) (Fig. 2). The term grade 1-2 FL is preferred as no significant clinical differences between grade 1 and grade 2 have been identified. Grade 3 is defined by the presence of

Table I. General diagnostic criteria to differentiate FL from RFH.

Morphologic Features	FL	RFH
Nodal architecture	Partially/totally effaced	Preserved
Number of follicles	High number, randomly distributed; uniform	Low; more numerous in the cortex
Follicles dark and light zone	Polarization lost	Polarization preserved
Follicles size and shape	Uniform; Regular	Variable; irregular; elliptical
Cellular composition of follicles	Monotonous	Heterogeneous
Mantle zone	Scant or absent	Well developed
Tingible body macrophages	Uncommon or absent	Many
BCL2 immunostaining of follicles	Positive (not always)	Negative
t(14;18)/IGH-BCL2	Present (80%)	Absent

Table II. FL grading according to updated 2017 4th WHO classification.

Grade	Proportion of centroblasts	Percentage
Grade 1-2 [Low grade FL]	0-15 centroblasts/HPF	80-90%
Grade 3A	> 15 centroblast /HPF (centrocytes present)	10-20%
Grade 3B	> 15 centroblasts/HPF (follicles entirely composed of large centroblasts)	Rare
DLBCL	> 15 centroblasts/HPF (area with diffuse pattern of growth; absence of CD21, CD23)	
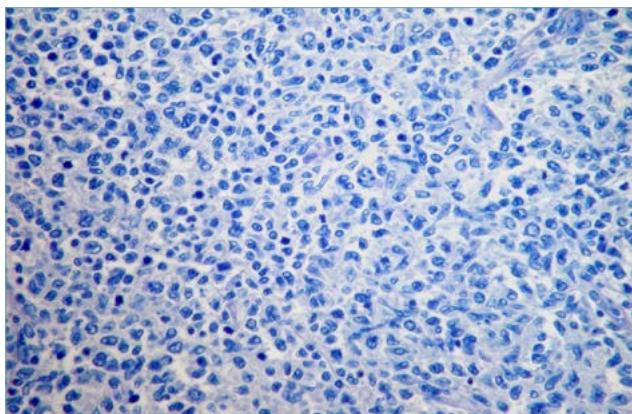
Figure 2. Lymph node. Follicular lymphoma, grade 1-2. Giemsa, 200x magnification.
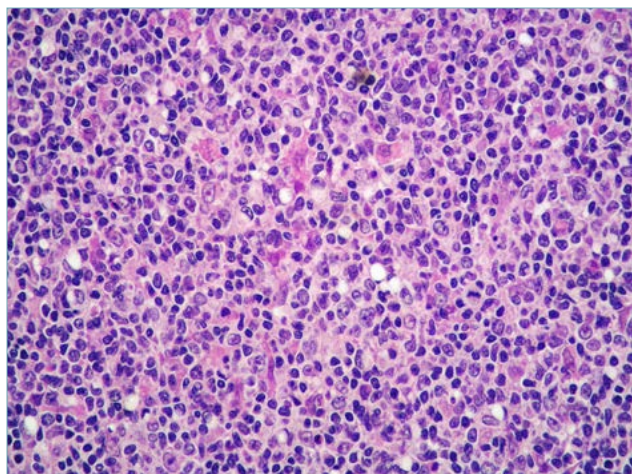
Figure 3. Lymph node. Follicular lymphoma, grade 3A. Giemsa, 200x magnification.

more than 15 centroblasts/HPF and it is subdivided in 3A (Fig. 3) and 3B, depending if centrocytes are present (3A) or not (3B) [1]. If distinct areas of grade 3 are present in an otherwise grade 1-2 FL, a separate diagnosis of grade 3 FL has to be made. Furthermore, the percentage (%) area of each grade has to be reported. Of note, the presence of a diffuse area with grade 3 cytology imposes a diffuse large B-cell lymphoma

(DLBCL) diagnosis (Tab. II) [1]. However, grading reproducibility is low and it has not been easily replaced by the Ki-67/MIB1 proliferation index. Many limitations affect the current grading system, as the following: i) FL may show considerable heterogeneity from area to area, then sampling of follicles is critical (accurate grading can therefore be difficult and not advisable on core needle biopsies); ii) follicles may show a range in cytological composition, so grade 1-2 and grade 3 follicles may coexist inside the same lymph node; iii) large centrocytes (large cleaved cells) or small centroblasts may be interpreted differently by individual pathologists; iv) counting centroblasts should be rigorous; v) poor tissue handling, fixation or technical processing problems may introduce artifacts interfering with grading. These factors underscore the highly subjective nature of FL grading with considerable inter-observer variation.

Currently, the proliferation index, assessed by Ki-67, is not included for grading. Nevertheless, every pathologist includes Ki-67 in the report. It is a useful practice because, although most FL grade 1-2 have Ki-67 < 20%, cases with low grading, but high Ki-67, do exist and may have a more aggressive behavior (identical to grade 3) [1]. Using Ki-67 may be troublesome, first because its distribution is not uniform throughout follicles. Further, we usually evaluate Ki-67 inside follicles only, excluding the interfollicular region. This may be the right approach for FL with predominant follicular pattern of growth. What is about FL with either mixed follicular/diffuse or entirely diffuse pattern? What is the right way to evaluate Ki-67 immunostaining in FL? To date, these are open questions. Finally, an important question is whether the histological grading system could be replaced or supplemented by a genetically oriented classification system, for instance by separating t(14;18)-positive FL from translocation-negative ones, although stratification of FL based solely on genetic features does not seem practical at present.

It is also recommended to specify in the pathology report the relative proportions of follicular and diffuse areas. A diffuse area is an area completely devoid of follicles without a follicular-dendritic-cell meshwork (confirmed by CD21 and CD23 negativity). In this setting, the WHO classification accepts low-grade FL

Table III. FL growth patterns.

Reporting pattern of growth in FL	(%) mention the percentage of each component in the report
Follicular	> 75%
Follicular and diffuse	25-75%
Focally follicular, predominantly diffuse	< 25%
Totally diffuse	0-NO follicular pattern

with an entirely diffuse pattern. Indeed, diffuse areas are not clinically relevant in low-grade 1-2 FL.

Differently, the presence of diffuse areas composed predominantly of centroblasts in FL of any grade requires a DLBCL diagnosis. The percentages of DLBCL and FL have to be reported (Tab. III). This situation may be summarized by examples of FL with a mixed follicular and diffuse pattern of growth, rich in centroblasts enough for grade 3.

For example: grade 3A FL 90% follicular pattern + 10% diffuse pattern, has to be reported as DLBCL (10%) + FL grade 3A (90%), following the updated 4th WHO classification 2017. Despite these strict criteria, there is much debate on this issue. Classify a small diffuse grade 3A area as DLBCL might sometimes appear overstated, in spite of WHO classification criteria. For the time being, it is not clear whether, and if so how, the above criteria could be easily translated into the reporting room next to microscope.

In situ Follicular Neoplasia (ISFN)/"Intrafollicular Neoplasia" or in situ follicular lymphoma and early partial nodal involvement by FL

"In situ FL" was initially reported in 2002 by Cong et al. [3]. Currently "in situ follicular neoplasia" (ISFN) is recognized as a FL variant in the updated 2017 WHO Classification [1]. It is defined as a clonal B-cell population, strongly expressing BCL2 and CD10, within GC of an otherwise reactive lymph node. The term ISFN is used to designate a condition in which the t(14;18)-positive cells are restricted to GC. It represents an incidental finding, often recognized with the aid of BCL2 and CD10 stainings, in the setting of reactive follicular hyperplasia. In a series of unselected reactive lymph nodes, Henopp et al. reported a prevalence of 2.3% for ISFN [4]. Its clinical significance is not yet fully understood. In their series of 13 ISFN cases, Montes-Moreno et al. identified 3 patients with overt FL, 1 patient developing full-blown FL 15 months after initial ISFN and 5 patients with B-cell lymphomas other than FL [5]. Furthermore, specific risk factors for disease progression are currently unknown [6.]

ISFN diagnosis is challenging and clinical implications are poorly defined. Histologically, ISFN usually shows a largely preserved nodal architecture, containing only very few neoplastic follicles in the background of reactive follicular hyperplasia [3]. In other terms, at low power these follicles may be quite subtle, not much different from surrounding reactive follicles. At medium and high power, neoplastic follicles are composed by a monotonous population of small, cleaved centrocytes. CD10 and BCL2 (Fig. 4) strongly positive cells are exclusively within GC lacking polarization, with intact mantle zone, and exhibiting decreased Ki-67, compared to reactive GC (Fig. 5). These follicles are usually positive for t(14;18) by FISH. In absence of an overt FL lymphoma, after careful clinical evaluation, a
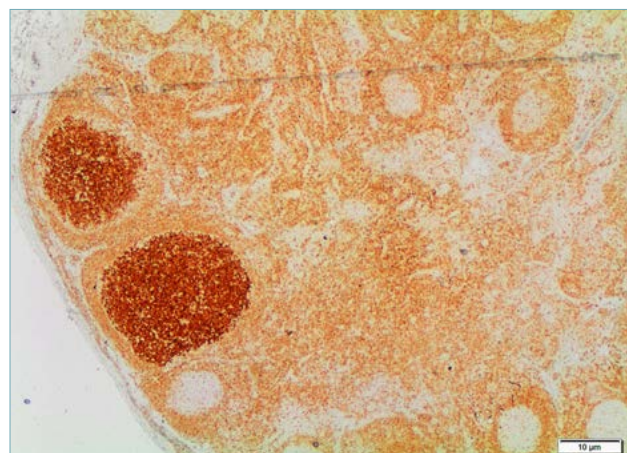

Figure 4. Lymph node. Two neoplastic Bcl2-positive follicles. Bcl2 immunostaining, 200x magnification.
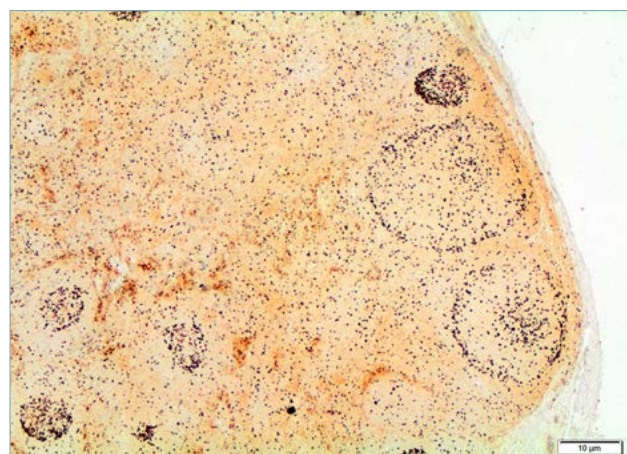

Figure 5. Lymph node. The two neoplastic follicles presented in Figure 4 show a low proliferation index (about 10-15%). Ki67/MIB1 immunostaining, 200x magnification.

Table IV. Diagnostic criteria for In Situ Follicular Neoplasia (ISFN).

1	Lymph node architecture is intact with prevalent follicular hyperplasia
2	Monomorphic cell composition of GC mainlycontaining small cleaved centrocytes without tingible-body macrophages and absence of follicular polarization
3	Strong simultaneous expression of both BCL2 and CD10 in the involved germinal center
4	Proliferation index by Ki-67/MIB1 lower than in normal reactive GCs
5	Neoplastic cells have the t(14;18)(IGH/BCL2) translocation
6	Absence of interfollicular invasion
7	Immunohistochemistry (BCL2 and CD10 stains) is mandatory for diagnosis

"*wait-and-see*" strategy appears to be a reasonable practice [7]. ISFN could represent FL at the very early stage of development, a sort of pre-neoplastic event, requiring a second hit for full-blown neoplastic transformation. On the other hand, normal follicles might be colonized by BCL2-positive small cleaved centrocytes, representing early intra-follicular involvement by systemic overt FL [8]. In patients with overt FL at other sites, this finding probably represents a subtle colonization of pre-existing follicles by FL cells. The borderland between ISFN and "early" interfollicular/partial nodal involvement by FL could be quite ambiguous [9]. To be diagnosed as ISFN the criteria reported in Table IV need to be fulfilled.

To differentiate early partial nodal involvement by FL from true ISFN, the most important feature is interfollicular infiltration, i.e. the presence of atypical CD10, BCL6-positive small cleaved centrocytes, extending beyond GC. Furthermore, in partial nodal involvement by FL, follicles are larger than in ISFN and usually cluster together, resulting in partially effaced nodal architecture. Immunostains for CD10 and BCL6 are the most useful tools in this setting. The presence of scattered CD10, BCL6-positive small atypical lymphocytes in the interfollicular zone is consistent with "early" interfollicular or partial nodal involvement by FL. Nevertheless, we should admit that, when "early" interfollicular/partial nodal involvement by FL is found, standardized histological criteria for differentiating whether it represents a "de novo" neoplastic population or subtle nodal involvement by overt FL cannot easily be determined.

FL with monocytoid (marginal zone) differentiation

Marginal zone differentiation occurs in about 8% of FL [10]. Nodal architecture is usually effaced by a nodular proliferation of neoplastic follicles. The periphery of follicles looks pale, being composed of cells with round, cleaved nuclei, clumped chromatin, inconspicuous nucleolus and abundant clear cytoplasm, consistent with monocytoid/marginal zone differentiation (Fig. 6). A common clonal origin for both neoplastic GCB-cells
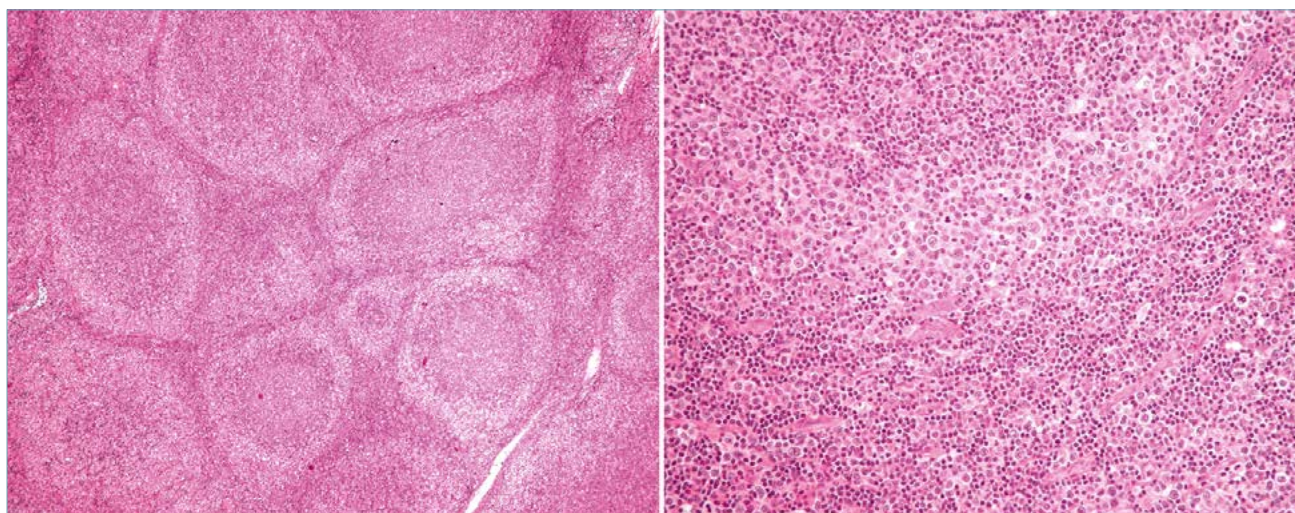

Figure 6. A Lymph node. Follicular lymphoma with marginal zone differentiation. The peripheral part of neoplastic follicles appears pale. HE, 100x magnification; B Lymph node. Follicular lymphoma with marginal zone differentiation. The periphery of neoplastic nodules is composed of medium-sized cells, with monocytoid features. HE, 200x magnification.
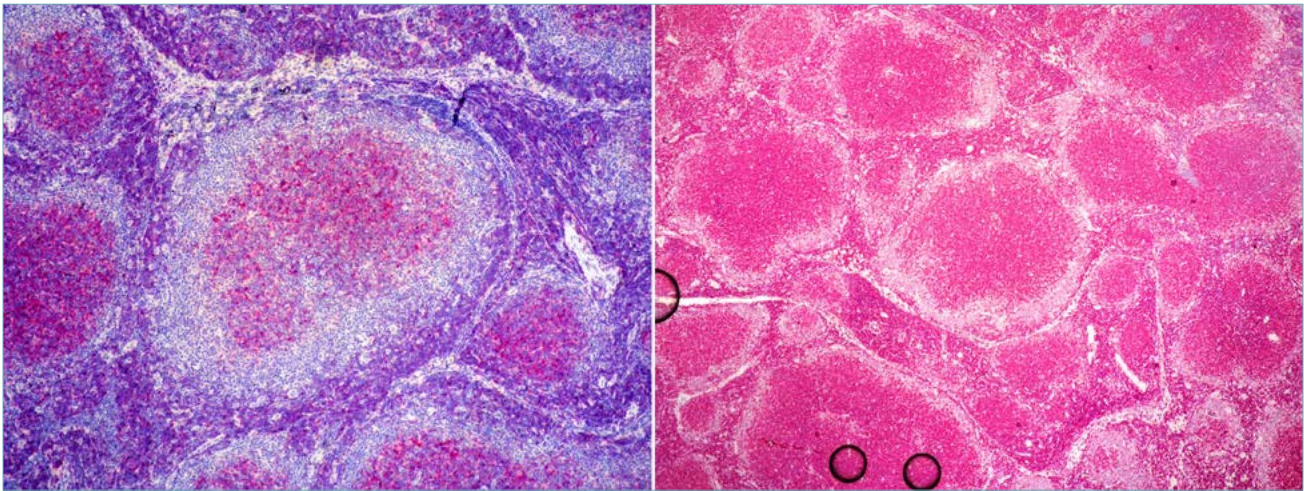
Figure 7. A Lymph node. Follicular lymphoma with marginal zone differentiation. The peripheral part of the neoplastic nodules lacks germinal center markers. CD10 immunostaining, 100x magnification; B Lymph node. Follicular lymphoma with marginal zone differentiation. The neoplastic follicle expresses Bcl2 molecule. Bcl2 immunostaining, 100x magnification.
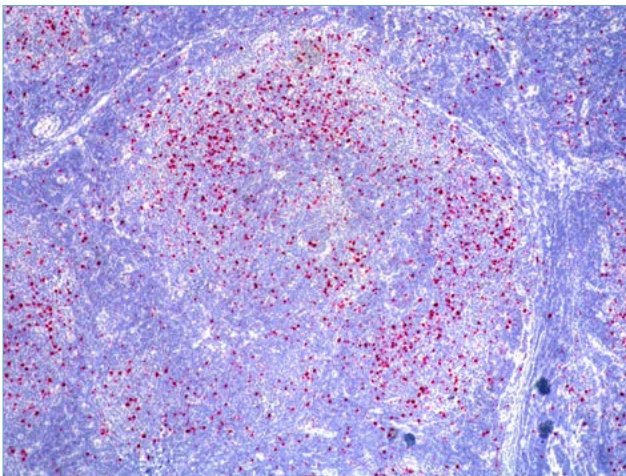

Figure 8. Lymph node. Follicular lymphoma with marginal zone differentiation. The proliferative index (Ki-67) is about 10-15%. The peripheral portion of the neoplastic nodule, with monocytoid features appear to be the most proliferative part.

and surrounding monocytoid B-cells is well documented [11] [12]. Neoplastic follicles express CD20, CD10, BCL6 and BCL2 (Fig. 7); differently perifollicular monocytoid B-cells are often CD10-negative and variably express BCL6. Ki-67/MiB1 confirms lack of polarization within neoplastic follicles (Fig. 8). Differentiating nodal marginal zone lymphoma (NMZL) from FL is not always straight forward [13]. In particular, differential diagnosis between FL with marginal zone differentiation and NMZL with prominent follicular colonization remains a challenge [14]. CD10, BCL6 and BCL2, routinely used in FL diagnosis,

could show variable expression. The strong co-expression of BCL2 and CD10 confirms the neoplastic nature of lymphoid follicles. As already mentioned, GC markers (CD10 and BCL6) may be expressed by neoplastic marginal zone-like B-cells, although these elements often lack CD10. The presence in the node of BCL2, BCL6 and CD10-positive follicles is a clue we are dealing with FL with prominent marginal zone differentiation. In absence of CD10, BCL2-positive neoplastic follicles and in cases negative for CD10, BCL6 and t(14;18), the use of new GC markers such as human germinal center-associated lymphoma (HGAL) and LIM-only transcription factor 2 (LMO2) may be useful. HGAL and LMO2 have been recently introduced in FL diagnosis [15]. HGAL is expressed in GC cells cytoplasm in the majority of FL (90%), regardless of grading (Fig. 9) [16]. All cases lacking CD10 and BCL2 express HGAL. HGAL is a useful marker in the diagnostic workup of problematic FL. LMO2 is expressed in 70% of FL (Fig. 10). The overall sensitivity of LMO2 as GC marker is similar to CD10 and BCL2 and superior to BCL6. As LMO2 is not downregulated in the interfollicular and diffuse FL components or in high grade FL, it is useful to identify FL lacking GC markers (CD10 and BCL6) and/or t(14;18).

Nevertheless, distinction between FL lacking t(14;18) and/or GC markers (CD10 and BCL6) and NMZL remains controversial. Indeed, differentiating NMZL colonizing follicles with residual CD10-positive GC cells from FL with marginal zone differentiation lacking CD10 and/or BCL6 can be very difficult, if not impossible. Furthermore, the lack of CD10 does not exclude FL, nor does its expression exclude NMZL, as CD10-pos-
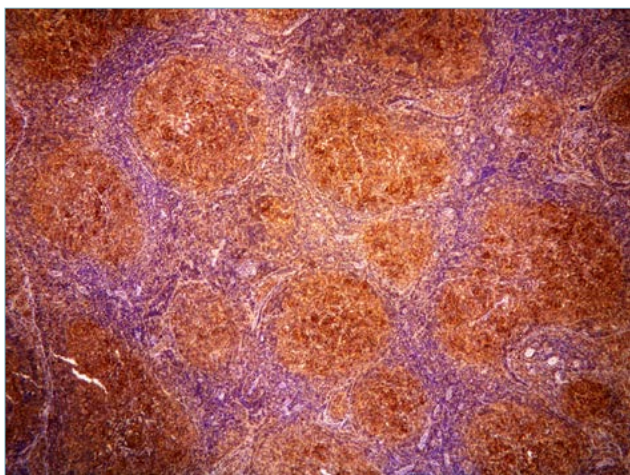
Figure 9. Lymph node. Follicular lymphoma. HGAL expression by the neoplastic nodule. HGAL immunostaining, 100x magnification.
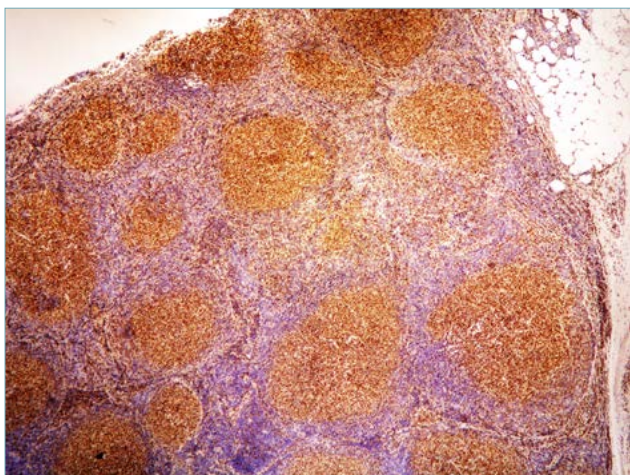

Figure 10. Lymph node. Follicular lymphoma. The neoplastic population is LMO2 positive. LMO2 immunostaining, 100x magnification.

itive NMZL rarely occurs [17]. Recent gene expression profiling and comparative genomic hybridization studies suggest FL lacking t(14;18) genetically resembles NMZL more than classical FL [18],[19]. Interestingly, FL with marginal zone differentiation is associated with chromosomal abnormalities (such as chromosome 3 trisomy) identified in NMZL and in t(14;18)-negative FL [20],[21]. Since fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), and next generation sequencing (NGS) analysis can be available, careful cytogenetic/molecular studies are sometimes invaluable for the correct classification.

FL with plasma cell differentiation

To date, plasmacytic differentiation has been reported in about 3% of FL [22]. It is well recognized that neoplastic GC B-cells may show post-GC maturation into memory B-cells and plasmacells [22-24]. Nevertheless, plasma cell differentiation is rarely seen in FL, presumably due to blocked differentiation. In FL with plasma cell differentiation, neoplastic B-cells show striking plasmacytic differentiation with interfollicular and intrafollicular distribution, as shown by light chain restriction. These neoplastic elements show features of mature plasmacells, expressing CD138, IRF4/MUM1, MUM18 and CD38. In FL with plasmacytic differentiation, centrocytes, centroblasts and plasma cells are clonally related and frequently carry BCL2 gene rearrangement [23]. Several other B-cell lymphomas like NMZL, lymphoplasmacytic lymphoma (LPL)/Waldenstrom's macroglobulinemia, chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL) may have plasmacytic differentiation, making the differential diagnosis with FL challenging. Indeed, NMZL with strong plasmacytic differentiation and prominent follicular colonization can be confused with FL with striking plasmacytic differentiation. Furthermore, high grade 3A or 3B FL with plasmacytic differentiation may be confused with DLBCL with plasmacytic differentiation. Careful morphological evaluation and immunoistochemical work-up, including HGAL, LMO2, CD5, CD23, LEF1, Cyclin D1, IRTA1, MNDA are mandatory in problematic cases. Polymerase chain reaction or FISH analysis for MYD88-L265P mutation is useful in diagnosing monomorphic small B-cell lymphoma with plasmacytic differentiation.

The presence of significant plasmacytic differentiation in FL may have clinical implications such as increased incidence of paraproteins, peripheral blood absolute lymphocytosis and higher clinical stage [24].

FL with signet ring cells

The term "signet-ring cell lymphoma" was introduced by Kim in 1978 to identify FL with clear cytoplasmic vacuoles, resembling mucin-producing signet-ring cell carcinoma (Fig. 11) [25]. Since then, the majority of lymphomas with signet-ring cells have been low-grade B-cell lymphomas, such as FL, MZL, LPL and SLL/CLL [26-29]. Rare DLBCL cases show signet-ring cells [30]. Peripheral T-cell lymphoma (PTCL) as well as anaplastic large-cell lymphoma (ALCL) can show cells with a signet-ring appearance (Fig. 12) [31]. The signet-ring cell FL represents an uncommon morphological variant. Histology shows small centrocytes admixed with
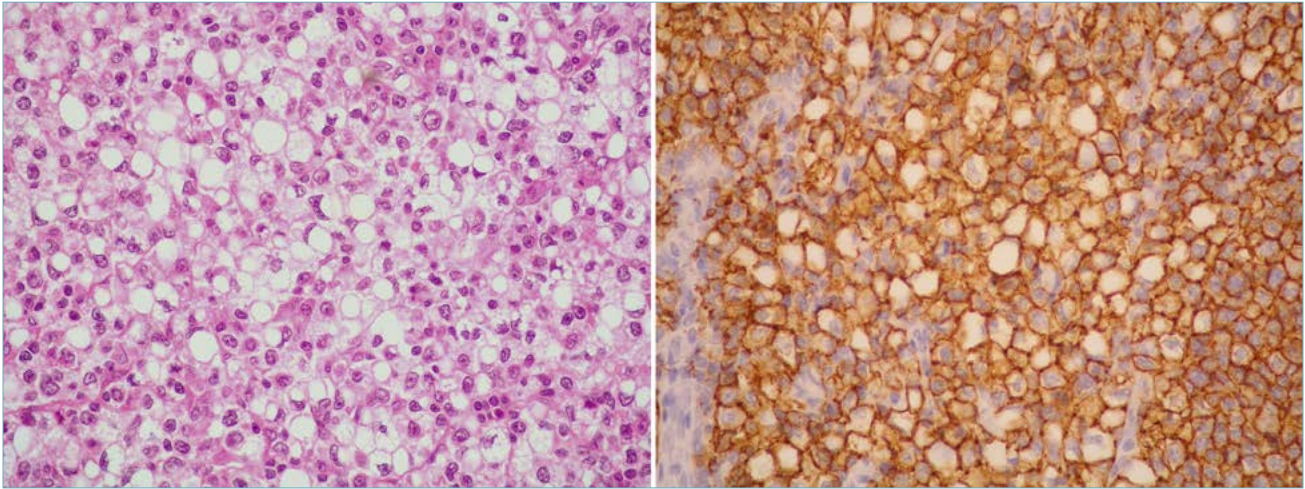
Figure 11. A Lymph node. Follicular lymphoma with signet ring cells. HE, 400x magnification; B Lymph node. Follicular lymphoma with signet ring cells. CD20 immunostaining, 400x magnification.
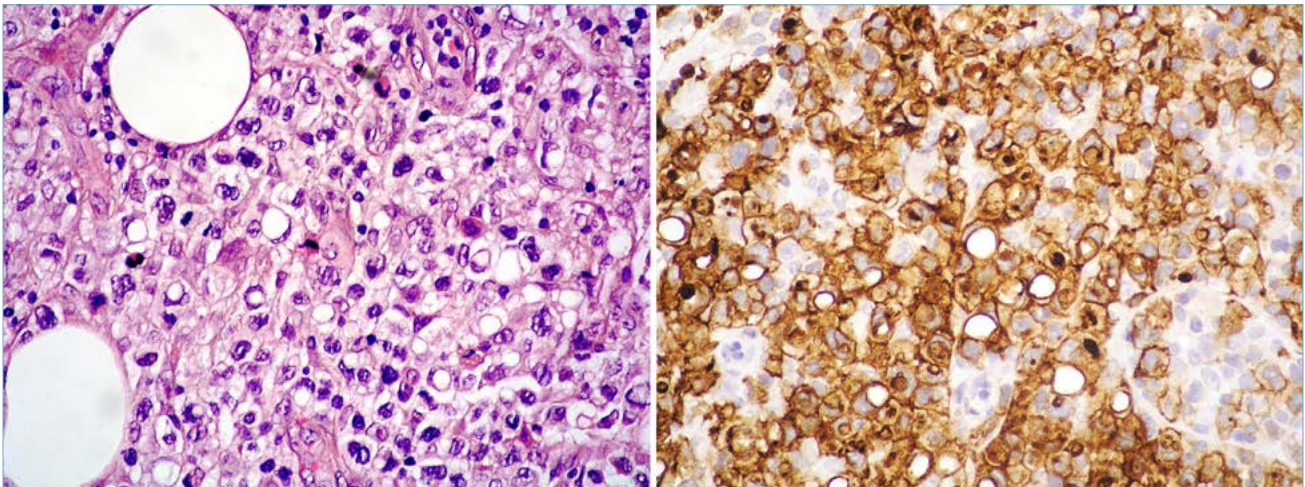

Figure 12. A Skin. Anaplastic large cell lymphoma with signet ring cells. HE, 400x magnification; B Skin. Anaplastic large cell lymphoma with signet ring cells. CD30 immunostaining, 400x magnification

large centroblasts; nuclei are indented by centrally located large cytoplasmic vacuoles. These cells are usually positive for CD20, CD10 and BCL6 and show immunoglobulin light chain restriction within cytoplasmic vacuoles. Signet-ring cell FL variant represents an extreme example of FL with striking plasmacytic differentiation [32],[33]. This morphological variant has to be recognized, avoiding misinterpretation as nodal metastasis of signet ring cell carcinoma, in which vacuoles are positive for mucin. Benign lesions, such as silicon and polivinilpirrolydone related lymphadenopathy, may assume a signet-ring cell morphology [34].

FL sclerosing variant

In 1975, Bennet concluded nodular sclerotic lymphosarcoma was a clinicopathologic variant of lymphoma with follicular center cell origin [35]. These cases were examples of the so-called sclerosing variant of FL. Extensive sclerosis is rather frequently seen in FL more than in other low-grade B-cell lymphomas. The majority of FL sclerosing variant occurs in retroperitoneal, mediastinal, or inguinal lymph nodes, but it can be seen in any lymph nodes and rarely at extranodal sites (Fig. 13) [36]. Histologically, nodal architecture is completely effaced by a nodular or diffuse
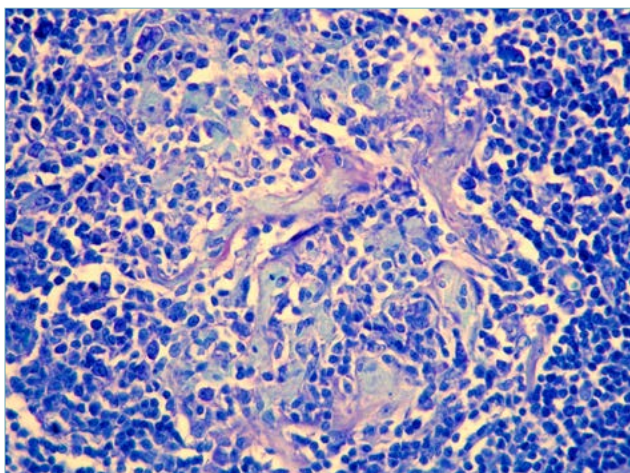
Figure 13. Lymph node. Follicular lymphoma sclerosing variant. Giemsa, 300x magnification.

lymphoid proliferation embedded in prominent sclerosis. Hyalinized collagenous bands separate tumor cells into clusters. Cytologically, neoplastic cells are small centrocytes admixed with large centroblasts positive for CD20, CD10, BCL6 and often BCL2-negative. IRF4/MUM1 is positive in grade 3A/3B FL. Two patterns of nodal fibrosis can be recognized. In the first one there is marked sclerosis with broad anastomosing and compartmentalizing collagenous bands, separating lymphoma cells aggregates and mimicking classic Hodgkin lymphoma (CHL), nodular sclerosis subtype. The second pattern displays delicate hyalinized collagenous bands with scattered "indian filing" lymphoid cells. Interstitial eosinophilic scleroialinosis is quite common, in particular in retroperitoneal FL [37]. The diagnosis of FL sclerosing variant may be challenging. As already mentioned the broad collagenous bands may mimic CHL, nodular sclerosis subtype. In CHL the typical inflammatory milieu, presence of Hodgkin/Reed-Sternberg cells (HRS) positive for CD30, CD15, PAX5 and Epstein-Barr virus by in situ hybridization encoded RNA (EBER) are helpful in the differential diagnosis. PTCL may show collagenous compartmentalization similar to sclerosing FL [38]. In PTCL collagenous bands are usually more delicate and associated with post-capillary venules proliferation, absent in sclerosing FL. Careful workup for T-cell markers should help in differentiating these neoplasms. Sometimes fibrosis in FL may be associated with prominent myofibroblastic differentiation, mimicking inflammatory pseudotumor of lymph node [39]. Whenever examining a nodal inflammatory pseudotumor-like lesion, follicular-dendritic cell or histiocytic neoplasms should be excluded as well as syphilis infection, by immunohistochemistry and Warthin-Starry stain. Finally, sclerosing FL histologically may mimic idiopathic retroperitoneal fibrosis (currently classified in the group of IgG4-related lesions) [37,40]. Attention to cytological details of small centrocytes and large centroblasts together with CD20, BCL2, GC markers and Ki-67 staining should easily differentiate sclerosing FL from idiopathic retroperitoneal fibrosis.

FL floral variant

Histologically, nodal architecture is effaced by an irregular, nodular proliferation, displaying the "floral-like" appearance (Fig. 14) [41]. The neoplastic follicles are typically surrounded by a prominent mantle zone, penetrating into the center of follicles. Pale and large follicles are infiltrated by darker mantle zone lymphocytes, producing the so-called "floral" appearance of follicles [41]. Most floral variant FL are grade 3A. This variant expresses CD10, BCL2, BCL6, supporting its GC origin, and rarely CD5 (FL floral variant CD5-positive) [42]. It has to be recognized because it closely mimics progressive transformation germinal centers (PTGC) and/or nodular lymphocyte predominance Hodgkin lymphoma (NLPHL). In NLPHL mantle zone B-cells may invade and totally disrupt follicles; follicular dendritic cell markers (CD21, CD23, CD35, and Podoplanin D2-40) reveal an expanded follicular dendritic cell meshwork and IgD immunostain identifies mantle zone B-cells. Scattered residual BCL6, CD10-positive GC cells are usually found.
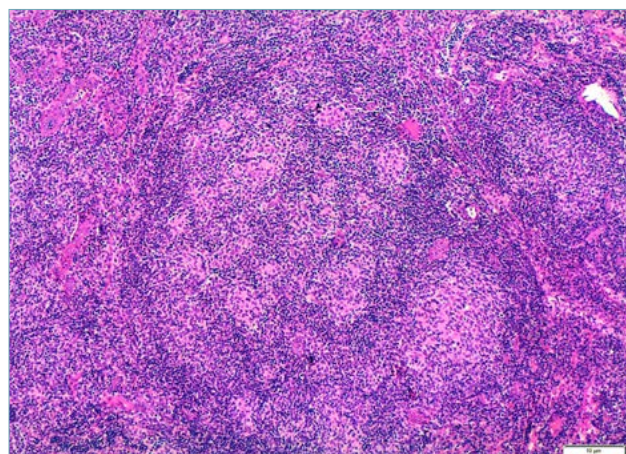

Figure 14. Lymph node. Follicular lymphoma floral variant. Giemsa, 100x magnification.

FL with abundant eosinophilic precipitate

FL with abundant extracellular PAS-positive protein-aceous, eosinophilic precipitate is a rare FL variant, initially reported by Rosas et al. in 1973 and later described by others [43-46]. Accumulation of amorphous, hyaline, non-amyloid material is a rare finding in other B-cell lymphoproliferative disorders such as RFH, plasma cell myeloma and dysimmune disorders [46]. FL with eosinophilic precipitate shows a nodal architecture totally effaced by neoplastic follicles containing amorphous eosinophilic PAS-positive and diastase-resistant extracellular material (Fig. 15).

Congo Red stain negativity excludes amyloid. The lymphoma cells are positive for CD20, BCL2, CD10 and BCL6. Both low-grade (grade 1, grade 2) and high-grade (grade 3A/3B) FL can show eosinophilic precipitate. Interestingly, the amorphous extracellular material is positive for CD20, suggesting it may represent B-cell membranes remnants. In 1973, Dorfman noted that nodular lymphomas contained PAS-positive eosinophilic material, appearing blue with Masson tri-chrome stain [47]. Ultrastructural studies confirmed that this material is not collagen, but rather accumulated membranous structures. These deposits must be differentiated from amyloid and stromal reactions described as hyalinosis, fibrosis, and orsclerosis [35,48,49]. Furthermore, since proteinaceous precipitates are often present within hyperplastic lymphoid follicles, a misdiagnosis of RFH could be made. The differential diagnosis between RFH and FL is often of great concern to pathologists and even more if follicles are composed mostly of eosinophilic deposits with only a few lymphoma cells.
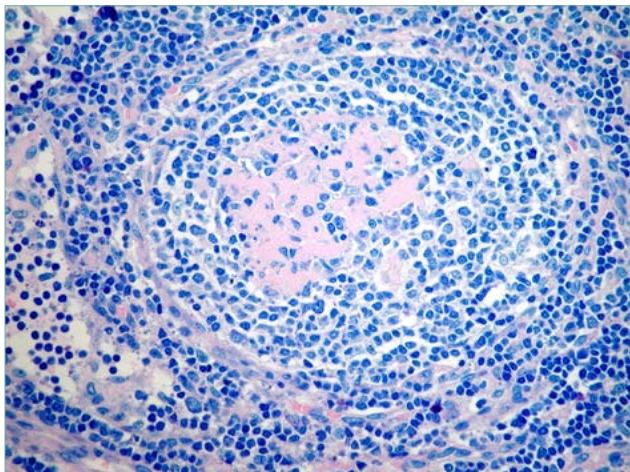
FL with spindle cells

Spindle cells have been described in very rare examples of FL. Microscopically, lymph node is effaced by predominantly spindle-shaped cells with elongated and slender nuclei. These cells are positive for GC markers (CD10, BCL2 and BCL6) [50].

FL variant containing numerous epithelioid cells

Granulomatous reaction is a rare finding in FL. In 1997 Naresh reported a prominent epithelioid granulomatous response in FL [51]. In this setting, trabecular fibrosis may also be present. More recently, Kojima et al. described FL with prominent epithelioid cell response. These epithelioid elements were in large aggregates, giving origin to a lymphoepithelioid lymphoma-like appearance [52].

Epstein-Barr Virus (EBV)-positive FL

Mackrides et al. reported some cases of EBV-encoded RNA (EBER)-positive FL. Most patients were elderly, with no other cause of immunodeficiency apart from age. Most cases were grade 3 FL, with high stage disease [53].

FL with high proliferation index Ki67MIB1

The prognostic significance of high proliferation index (Ki-67) in low-grade (grade 1-2) FL is controversial [54]. Some FL are low-grade (LG), according to the centroblast count, but show a high proliferation index (PI). For such cases, in addition to WHO grading, it is recommended to make the comment that LG-FL with high Ki-67 might pursue a more aggressive clinical course.

The optimal Ki-67 cut-offs for stratifying patient prognosis is not clear, but from the few data reported so far the Ki-67 cut off should be 30% [54]. The observations that LG-FL with high PI show a significantly worse disease specific survival (DSS) than those with a low PI suggest that these cases should be identified and distinguished from conventional LG-FL [54].

Figure 15. Lymph node. Follicular lymphoma with abundant proteinaceous material within germinal center. Giemsa, 400x magnification.

FL with blastoid features

The term "blastoid" refers to cytological features reminiscent of precursor cells. It is usually used to describe medium-sized cells with finely distributed chromatin and occasional small nucleoli. A reproducible definition of "blastoid features" is not easy to give, since cell size can vary from small to medium, and degree of chromatin immaturity is variable. FL with "blastoid" morphology, partly follicular pattern of growth, low mitotic index, and low Ki67 have been described [55]. Since the category of "blastoid" FL is not well reproducible, the working diagnosis of "FL not gradable, with blastoid features" is recommended.
Rare double-hit (DH) FL have been identified in cases with "blastoid"morphology [56].

Double-hit FL

Occasionally, de novo DH-FL have been reported (Fig. 16) [57-59]. According to recent studies, DH-FL often have high-grade histology (grade 3), high MYC protein expression and high MYC/IGH fusion [59]. Compared with high-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements, the genomic profile of DH-FL shows fewer copy-number alterations (Fig. 17) [59]. Unlike high-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements, which show a poor outcome and do not respond to conventional chemotherapy, the prognostic significance of DH-FL is still controversial. Miao et al. suggested that DH-FL has an aggressive behavior [57]. Yoshida

et al. and Miyaoka et al. reported that DH-FL tends to be less aggressive than high-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements [58,59].

Predominantly diffuse FL variant

In 2009 Katzenberger et al. proposed a distinctive variant of low-grade (grade-1-2) nodal FL, with predominantly diffuse architecture, frequent inguinal lymph node involvement, low clinical stage, lack of t(14;18)/IGH-BCL2 translocation, presence of chromosome 1p36 deletion or TNFRSF14 mutations and CD23 expression [60]. Morphologically, it is composed of CD20, CD10, and BCL6- positive centrocytes and centroblasts. Rare cases of CD10-negative diffuse FL may also occur, making the differential diagnosis from NMZL quite difficult. By definition, it has a diffuse pattern of growth, but contains very small reactive-appearing follicles in the background, negative for BCL2. CD23 expression by neoplastic B-lymphocytes is typically present in this variant [61]. Presence of diffuse, uniform CD23 expression in the context of bulky inguinal disease, centrocytic/centroblastic morphology and expression of at least one GC marker, assist in the diagnosis. The genetic landscape of predominantly diffuse FL is very distinct from conventional t(14;18)-positive FL [62]. The high prevalence of mutations in STAT6, CREBBP and KMT2D favors the follicular rather than marginal cell of origin. In particular, STAT6 mutations in the majority of diffuse FL variant (80%) suggests the potential importance of JAK/STAT6 pathway in lymphoma genesis. Further
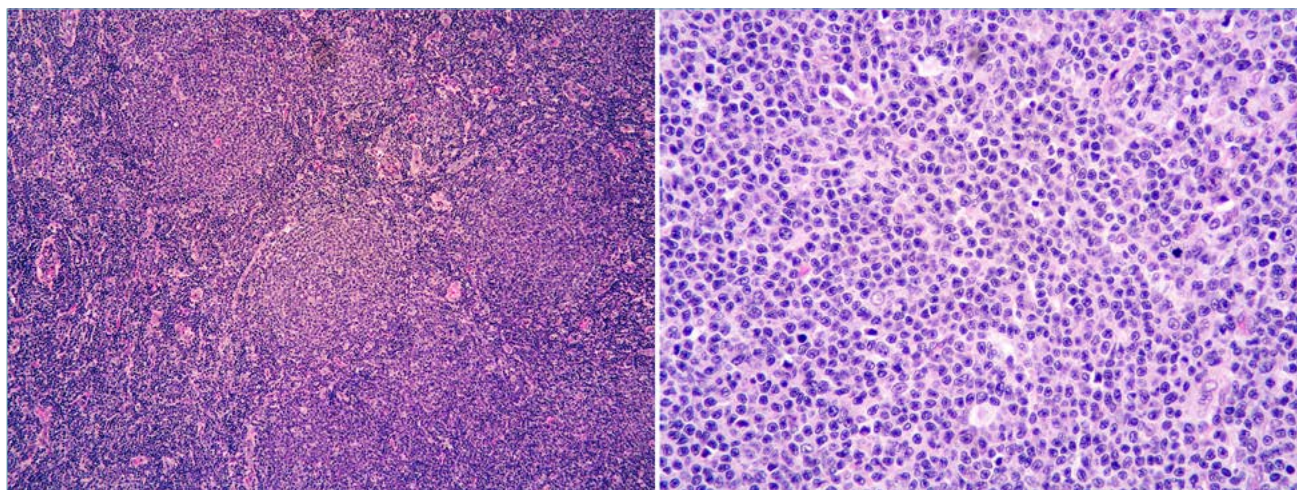

Figure 16. A Lymph node. Double hit follicular lymphoma, with follicular pattern of growth. Giemsa, 100 x magnification; B Lymph node. Double hit follicular lymphoma. Giemsa, 400 x magnification.
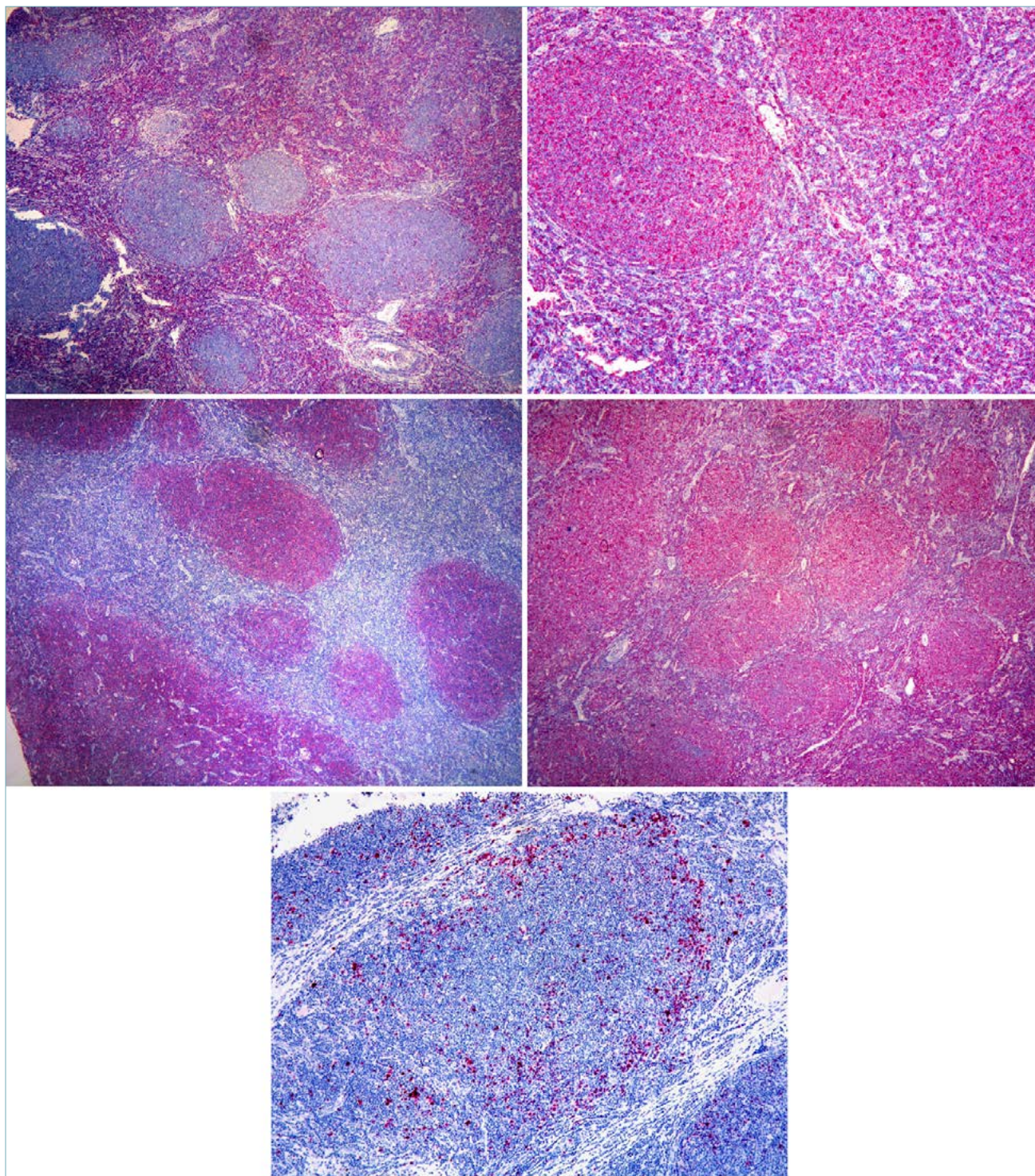
Figure 17. A Lymph node. Double hit follicular lymphoma. CD30 immunostaining, 40 x magnification; B Lymph node. Double hit follicular lymphoma. CD20 immunostaining, 100 x magnification; C Lymph node. Double hit follicular lymphoma. CD10 immunostaining, 40 x magnification; D Lymph node. Double hit follicular lymphoma. Bcl2 immunostaining, 100 x magnification; E Lymph node. Double hit follicular lymphoma. Ki-67/MIB1 immunostaining, 100 x magnification.

studies are required to better understand the relevant targets of STAT6, which interestingly include CD23.

Pediatric-type FL

FL is rare in children and adolescents. FL occurring in childhood can either resemble FL in the adults (adult-type FL in children) or it can be a rather distinct entity, recognized in the current WHO Classification as pediatric-type FL (PTFL) [1]. This entity, mainly seen in children and young adults, is biologically and clinically distinct from common FL [63,64]. It shows marked male predominance and the median age at presentation is 15-18 years, with rare cases in patients over 40. PTFL is usually an indolent disease, presenting in stage I with isolated adenopathy in the head and neck region, although axillary and/or inguinal adenopathy may be found. Furthermore, PTFL differs from the adult counterpart morphologically, immunophenotypically and genetically [65].

In PTFL nodal architecture is often totally effaced by large expansile, serpiginous and confluent follicles, with starry-sky pattern, mimicking florid follicular hyperplasia. The mantle zone is thin or absent. Follicles lack polarization. At high magnification, follicles are composed of monotonous medium-sized lymphoid cells of 10 with "blastoid" morphology (Fig. 18). Classical centroblasts may be present. High grade cytology is common. Ki-67 proliferation index is moderate or elevated (more than 30%). Grading is usually not applied. Neoplastic cells express GC markers such as CD10 and BCL6, whereas BCL2 is typically negative or weakly positive in a minority of cases. MUM1/IRF4 is negative; in case of strong MUM1/IRF4 expression, large B-cell lymphoma with IRF4 rearrangement
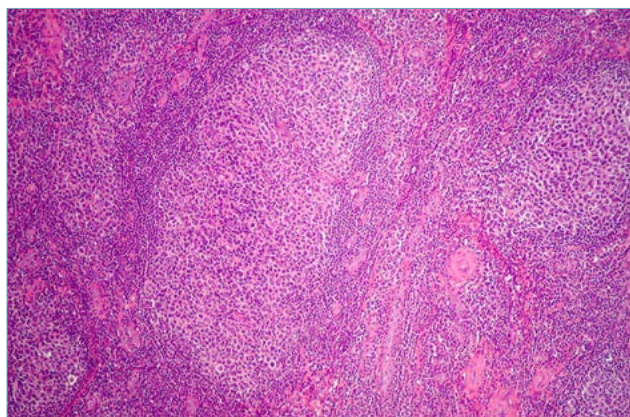

Figure 18. Lymph node. Follicular lymphoma, pediatric-type. HE, 200x magnification.

Table V. Diagnostic criteria for pediatric-type FL.

1	Expansile, serpiginous and/or confluent follicles with starry-sky pattern, absence of polarization and attenuated mantle zone; sometimes nodal tissue gives the appearance of "a node within a node"
2	High-grade cytology with "blastoid" cells
3	High proliferation index by Ki67/MIB1
4	Lack of BCL2 expression and t(14;18)(q32;q21) IGH/BCL2 gene rearrangement

has to be considered. Furthermore, FISH analysis is negative for t(14;18)IGH-BCL2, BCL6 as well as for IRF4 genes rearrangements. Immunoglobulin gene rearrangements either kappa or lambda are present. Overlap with florid RFH remains a practical problem. PCR analysis for IGH/IGK/IGL gene rearrangements is strongly recommended in the diagnostic work up of PTFL. The majority of cases diagnosed in the past as "atypical clonal florid follicular hyperplasia" and/or "follicular hyperplasia with giant follicles", almost certainly represent cases of true PTFL. The mutational landscape of PTFL differs from that of typical FL. Thus, genomic differences may distinguish PTFL from usual FL. Studies using whole-exome sequencing and NGS technology discovered that PTFL has a unique mutational profile, including TNFRSF14 and MAP2K1 mutations. Furthermore, mutations in many genes recurrently altered in common FL are absent in PTFL, suggesting a distinctive biology [66,67]. In other words, PTFL is a lymphoma with low malignant potential, indolent course and very low genomic complexity [67]. PTFL patients are usually managed conservatively and have excellent event-free survival with surgical node excision alone. Strict criteria must be followed in PTFL diagnosis as illustrated in Table V. Cases with similar characteristics may occasionally be seen in young adult [68]. However, according to WHO classification, PTFL should be diagnosed with caution in patients over 25 years, as distinction from usual FL grade 3A-3B can be difficult. On the other hand, as previously mentioned, not all FL in children or young are PTFL.

Large B-cell lymphoma with IRF4 Rearrangement

A subset of large B-cell lymphoma occurring in children and young adults is associated with translocation of IRF4 gene at chromosome 6p25.3 recognized by FISH [69]. Palatine tonsil, Waldeyer ring and head and neck lymph nodes are commonly involved. Histologically, it can be completely diffuse, completely follicu-

lar or follicular and diffuse. It is composed of medium-sized to large cells and unlike PTFL, follicles do not have a serpiginous appearance and a starry-sky pattern is absent. Neoplastic cells strongly express MUM1/IRF4 and are BCL6-positive. CD10 and BCL2 are positive in 66% of cases [1]. Ki-67 is usually high. The outcome is favorable after immunochemotherapy with or without radiotherapy, unlike PTFL which follows a good clinical course with the only surgical node excision.

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