Review

The broad landscape
of follicular lymphoma: Part II

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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 it 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 is 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 the patient outcomes and treatment.

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

Introduction

Follicular lymphoma (FL) is the most common low-grade mature germinal center B-cell lymphoma in Western countries, representing 20% to 30% of all non-Hodgkin lymphomas [1]. The updated 2017 World Health Organization (WHO) Classification includes critical aspects about FL [1]. In recent years, histological and clinical spectrum of germinal center derived B-cell neoplasms has expanded, leading to the conclusion that FL represents a far more heterogeneous entity than originally appreciated. In the previous review we illustrated FL variants encountered in diagnostic practice [2]. Surgical pathologists and hematopathologists should be aware of the broad FL landscape, in order to avoid diagnostic pitfalls and get to more accurate diagnosis.

Although FL is mostly a nodal disease, it can involve primarily extranodal sites. In the current WHO classification, it is well recognized that FL aris-

ing at particular extranodal sites (i.e. duodenum, skin and testis) have clinicopathological features and outcomes different from conventional nodal FL [1]. The skin and gastrointestinal (GI) tract are the most commonly involved extranodal sites. The site of involvement may affect disease prognosis [3]. It is well recognized that stage I FL of the skin and duodenal-type FL have a significantly better outcome than nodal primary disease. Differently, stage I FLs of muscle, connective tissue and nervous system have significantly worse survival than nodal FLs. Other extranodal sites such as head and neck or respiratory system are not associated with worse survival.

Duodenal-type FL

Primary duodenal FL is a variant with distinctive biological and clinical features. It consists of polypoid lesions of the small bowel, more often in the second portion of duodenum [4]. Patients are usually asymptomatic. The disease is localized and incidentally detected. Classically, small nodules involve mucosa and submucosa. The cellular composition recapitulates low-grade FL, with centrocytes and only rare centroblasts (Fig. 1). The cells are positive for CD10, CD20, BCL6 and BCL2 and carry t(14;18)/IGH/BCL2 (Fig. 2). Primary duodenal FL has an indolent clinical course, often without therapy. Radiotherapy can be used. Local recurrences can occur. Clinical evaluation and staging is essential to exclude systemic FL secondarily involving the bowel, which follows a more aggressive course [5].

Figure 2. A Ileum. Follicular lymphoma, duodenal-type. CD20 immunostaining, 100x; B Ileum. Follicular lymphoma, duodenal-type. BCL6 immunostaining, 100x; C Ileum. Follicular lymphoma, duodenal-type. BCL2 immunostaining, 100x; D Ileum. Follicular lymphoma, duodenal-type. KI67/MIB1 immunostaining, 100x.

In this setting, multiple lymphomatous polyposis (MLP) needs to be mentioned, which is a rare clinical presentation of primary gastrointestinal lymphomas. MLP patients typically present multiple polypoid lesions of different sizes throughout the gastrointestinal tract. Most cases are mantle cell lymphoma (MCL), others originate from mucosa-associated lymphoid tissue (MALT lymphoma) and a few cases are FLs [6-8].

Testicular FL

Primary testicular FL was initially described in children and subsequently in adults (Fig. 3) [9,10]. It is usually a low stage disease (stage 1E). Histologically, it tends to show high-grade morphology (grade 3A) and the pattern of growth can be follicular or follicular and diffuse. Prominent fibrosis is often present. (Fig. 4). Testicular FL expresses germinal center (GC) markers (CD10, BCL6), but it usually lacks BCL2-protein expression and BCL2 gene rearrangements (Fig. 5). FL of the testis is typically a localized disease with an indolent clinical behavior and good prognosis. Optimal therapy for patients with low stage disease is not well defined. Most patients (children and adults) are treated with surgery plus anthracycline-containing chemotherapy, sometimes with central nervous system prophylaxis. In adults, primary FL of the testis needs to be distinguished from diffuse large B-cell lymphoma (DLBCL)
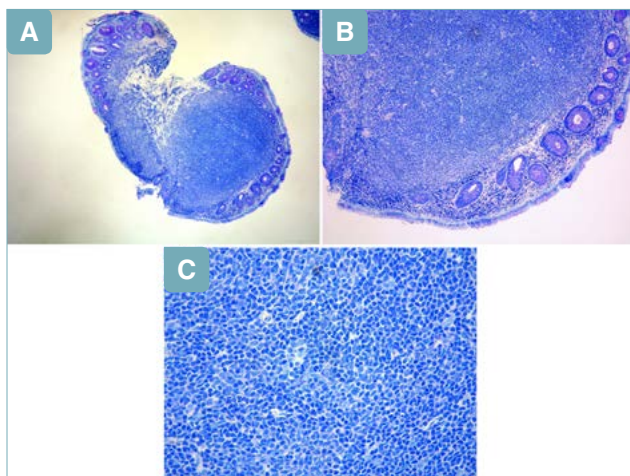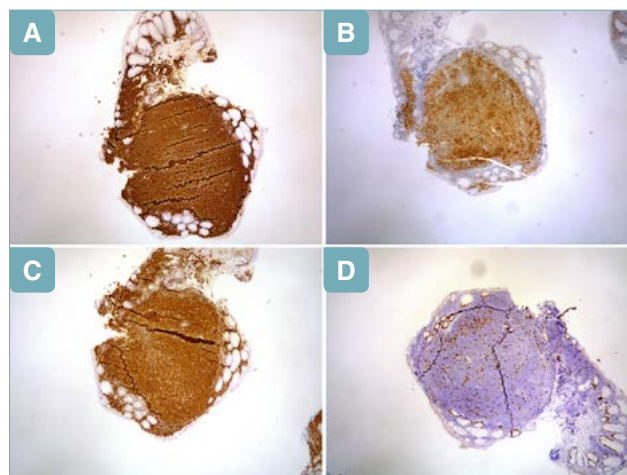

Figure 1. A Ileum. Follicular lymphoma, duodenal-type. Giemsa, 100x; B Ileum. Follicular lymphoma, duodenal-type. Giemsa, 200x; C Ileum. Follicular lymphoma, duodenal-type. Giemsa, 400x.

Figure 3. Testis. Primary follicular lymphoma of the testis. Gross appearance. Courtesy of Dr. A. Pireddu, Anatomia Patologica, Ospedale di Città di Castello, Perugia, Italy.
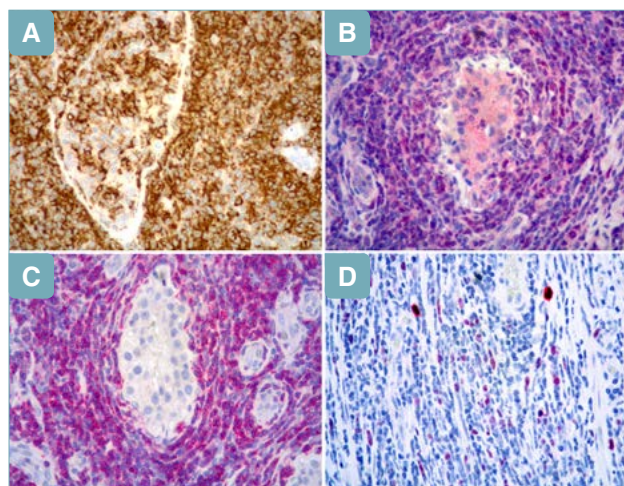

Figure 5. A Follicular lymphoma of the testis. CD10 immunostaining, 400x; B Follicular lymphoma of the testis. BCL6 immunostaining, 400x; C Follicular lymphoma of the testis. BCL2 immunostaining, 400x; D Follicular lymphoma of the testis. Ki-67/MIB1 immunostaining, 400x.
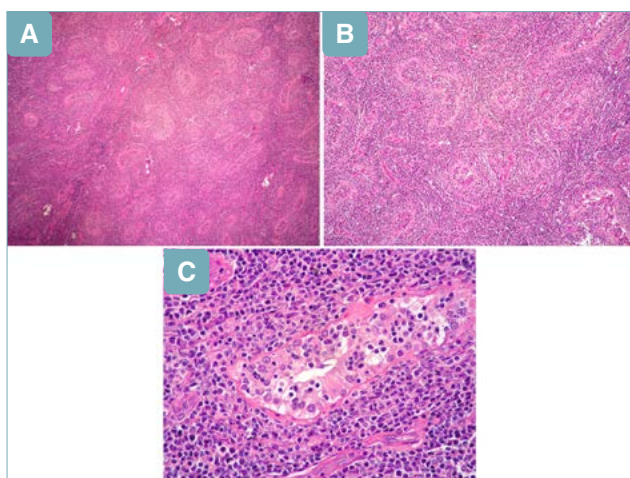

Figure 4. A Follicular lymphoma of the testis. HE, 100x; B Follicular lymphoma of the testis. HE, 200x; C Follicular lymphoma of the testis. HE, 400x.

(more commonly seen in the adult testis), which is a much more aggressive disease.

FL confined to the ovaries

FL arising primarily in the ovary is very rare and its clinicopathological features are not completely clear. Oznan et al. identified two main groups of FL arising in the ovary with divergent clinicopathological aspects [11]. The first group included cases with high-grade histology (3A), negativity or weak positivity for BCL2 and absence of BCL2 translocation; this group frequently had low stage disease. The second group included cases with low histological grade, strong positivity for BCL2 protein and presence of IGH/BCL2 translocation; this group frequently had advanced stage disease. There is no clear evidence that the second group arises primarily in the ovary, as the disease is usually in an advanced stage. The first group (high-grade, low stage) includes cases with disease usually confined to the ovary. This latter group may represent true primary ovarian FL. The features of high-grade, low stage BCL2-negative FL resemble those reported in FL of the testis, which shows a favorable outcome. It is tempting to speculate that this group of ovarian FL might be related to either pediatric-type FL (PTFL) or testicular FL [11].

Primary cutaneous FL

Primary cutaneous FL (PCFL) is a low-grade lymphoma of follicle center B cells, without evidence of systemic/nodal involvement at time of diagnosis. It is the most common primary cutaneous B-cell lymphoma. It presents with localized plaques or nodules on the scalp, trunk and back and rarely on the legs; multifocal skin lesions can be present. PCFL involves the dermis, often extending into subcutis. The epidermis is spared with a grenz zone separating the epidermis from the

underlying lymphoid proliferation (Fig. 6). Follicular and diffuse or totally diffuse pattern of growth may be present (Fig. 7) [12]. Neoplastic follicles are usually closely packed, irregular and not polarized, tingible body macrophages are absent, and mantle zone is thin or absent. Neoplastic cells include centrocytes and centroblasts. Rarely, centrocytes may be spindle-shaped or show bizarre features with different sizes and shapes [12]. Sclerosis and myxoid features may also be present in PCFL, particularly in the spindle cell variant [12]. Reactive T cells can be prominent. PCFL with a diffuse pattern of growth is entirely composed of sheets of centrocytes and centroblasts. The neoplasm may show any grade, although high-grade cytology (grade 3) is seen quite frequently and differential diagnosis with DLBCL legtype is mandatory. BCL6 is positive; CD10 is positive in cases with a follicular growth pattern, whereas it is often negative in cases with predominantly diffuse pattern (Fig. 8) [13]. Although BCL2 is often reported as negative or weakly positive and t(14;18)/IGH-BCL2 is frequently absent, recent studies have identified BCL2 expression as well as the presence of BCL2 rearrangements in a

proportion of PCFL [14,15]. IRF4/MUM1 and FOXP1 are usually absent. Ki-67 shows a low proliferation index. Some PCFLs, mainly those composed of large cells and which need to be distinguished from DLBCL legtype, can show high Ki-67. PCFL patients usually have an indolent disease, regardless of grade. Unlike nodal FL, PCFL should not be graded histologically, because grading does not seem to provide prognostic information. Surgical excision and local radiotherapy are treatments of choice for localized disease. Rare cases with multifocal skin lesions and extensive cutaneous disease require systemic therapy. Local recurrences are reported (20-30% of cases). When extracutaneous sites are involved, regional lymph nodes and bone marrow are usually affected [12]. Transformation to DLBCL has been suggested by some studies [16].

Systemic FL secondarily involving the skin needs to be excluded. This scenario is challenging for pathologists, because careful clinical workup and staging are usually unavailable at time of skin biopsy. PCFL with diffuse pattern and numerous large centrocytes and centroblasts can be tricky to separate from DL-
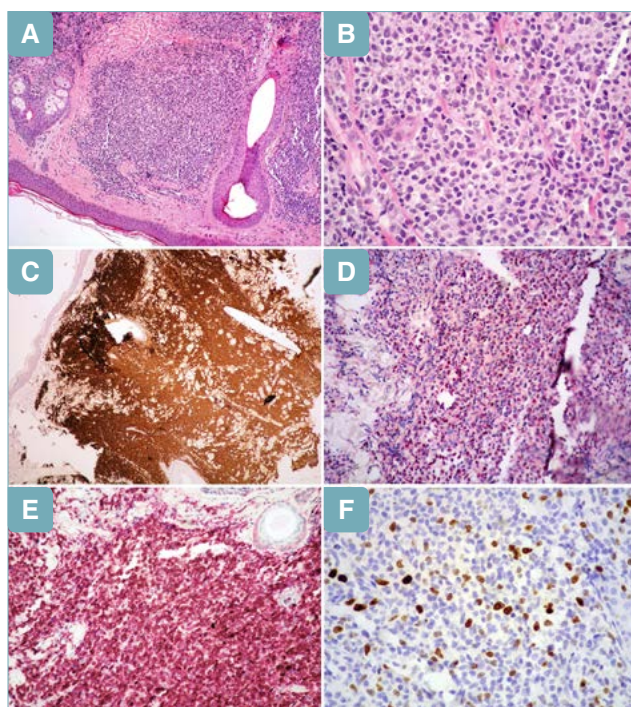

Figure 6. A Primary cutaneous follicular lymphoma. HE, 200x; B Primary cutaneous follicular lymphoma. HE, 400x; C Primary cutaneous follicular lymphoma. CD20 immunostaining, 100x; D Primary cutaneous follicular lymphoma. BCL6 immunostaining, 100x; E Primary cutaneous follicular lymphoma. BCL2 immunostaining, 100x; F Primary cutaneous follicular lymphoma. Ki-67/MIB1 immunostaining, 400x.

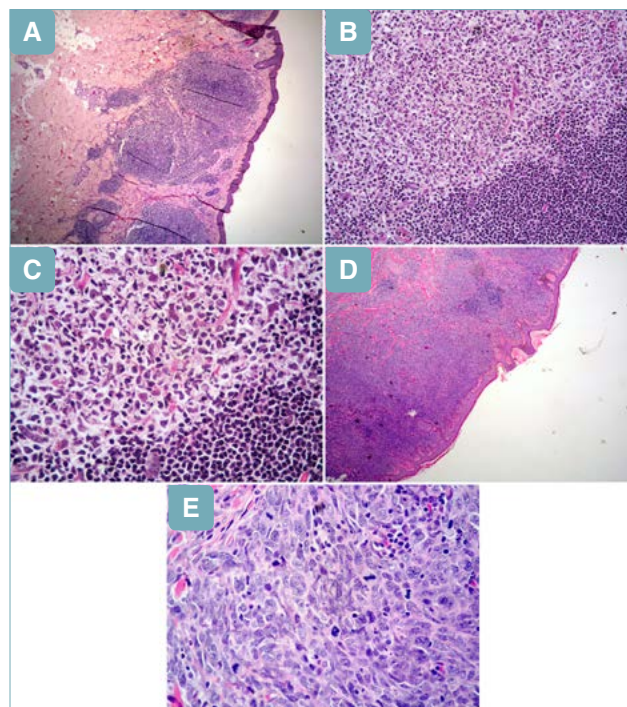**Figure 7.** A Primary cutaneous follicular lymphoma, follicular pattern of growth. HE, 100x; B Primary cutaneous follicular lymphoma, follicular pattern of growth. HE, 200x; C Primary cutaneous follicular lymphoma, follicular pattern of growth. HE, 400x; D Primary cutaneous follicular lymphoma, diffuse pattern of growth. HE, 40x; E Primary cutaneous follicular lymphoma, diffuse pattern of growth. Large-sized neoplastic cells. HE, 400x.
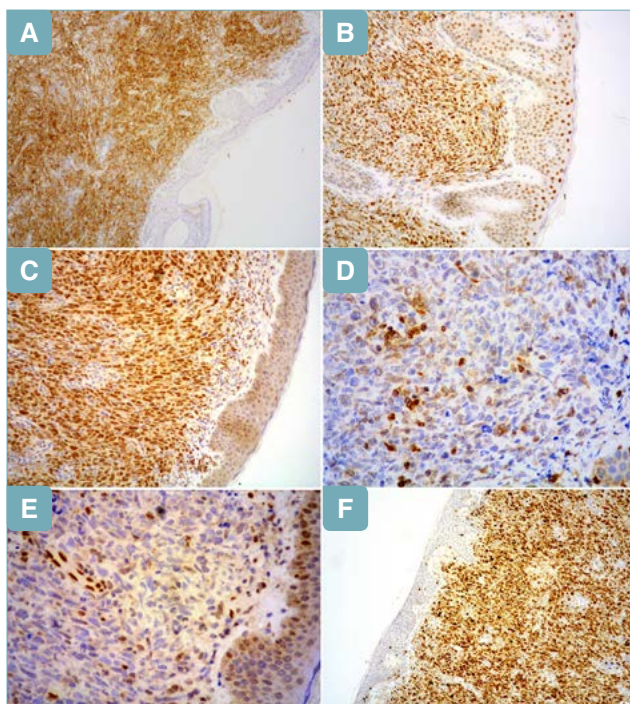
Figure 8. A Primary cutaneous follicular lymphoma, diffuse pattern of growth. CD10 immunostaining, 100x; B Primary cutaneous follicular lymphoma, diffuse pattern of growth. Large-sized neoplastic cells. BCL6 immunostaining, 200x; C Primary cutaneous follicular lymphoma, diffuse pattern of growth. Large-sized neoplastic cells. LMO2 immunostaining, 200x; D Primary cutaneous follicular lymphoma, diffuse pattern of growth. Large-sized neoplastic cells. BCL2 immunostaining, 400x; E Primary cutaneous follicular lymphoma, diffuse pattern of growth. Large-sized neoplastic cells. FOXP1 immunostaining, 400x; F Primary cutaneous follicular lymphoma, diffuse pattern of growth. Large-sized neoplastic cells. KI-67/MIB1 immunostaining, 200x.

Figure 9. A Skin. Marginal lymphoma. Small, medium-sized lymphoid cells and few mature plasma cells. HE, 200x; B Skin. Marginal lymphoma. Monotypic mature plasma cell component. Kappa immunostaining, 200x; C Skin. Marginal lymphoma. Monotypic mature plasma cell component. Lambda immunostaining, 200x.

BCL leg-type. The presence of centrocytes, follicular dendritic cells meshwork and numerous T cells argue in favor of PCFL. Sheets of large atypical centroblasts and/or immunoblasts support DLBCL leg-type. MUM1 and FOXP1 are usually absent in PCFL, differently from DLBCL leg-type [12].

Primary cutaneous marginal zone B-cell lymphoma (PCMZBCL) needs to be distinguished from PCFL (Fig. 9). It shows a nodular or diffuse infiltrate within the dermis and sometimes subcutis, with sparing of epidermis. At low power, PCMZBCL typically shows nodular infiltrates containing reactive GC surrounded by small- and medium-sized cells with pale cytoplasm (marginal-zone, centrocyte-like cells). Characteristically, PCMZBCL has a more heterogeneous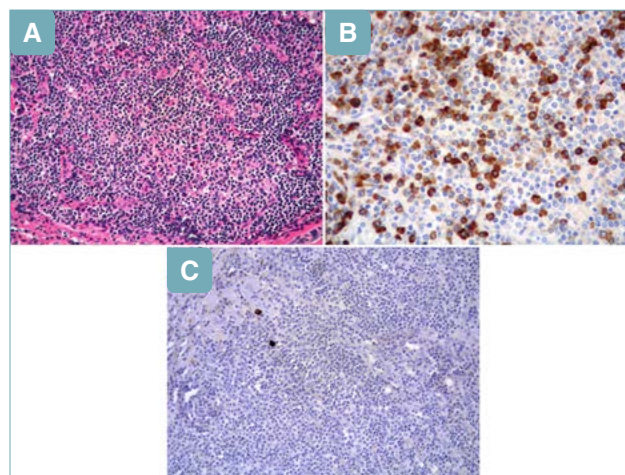 cytological appearance, including small- to medium-sized mature centrocyte-like lymphocytes, monocytoid lymphocytes with abundant clear cytoplasm and plasma cells. Dutcher bodies may be identified. PCMZBCL lacks expression of BCL6, CD10, and CD5. Light chain restricted plasma cells are commonly found at the periphery of the lesion [17].

Primary cutaneous follicular helper T-cell lymphoma (PCFHTCL) is a relatively recently described lymphoma mimicking PCFL. Patients tend to be elderly, presenting with multiple nodules, papules and/or plaques, often involving the extremities [18]. PCFHTCL displays a nodular architecture, syringotropism and includes numerous B cells. A careful examination reveals atypical T-cells with a follicular T-helper phenotype, including CD10 and BCL6 [19]. Systemic nodal follicular T-cell lymphoma may secondarily involve the skin; it can mimic follicular B-cell lymphoma.

Blastic plasmacytoid dendritic cell neoplasm is a rare myeloid neoplasm of immature plasmacytoid dendritic cells, commonly involving the skin. It can have a leukemic presentation or it can be limited to the skin, at least initially (Fig. 10). It follows an aggressive course, even in patients with skin-limited lesions. It may show a nodular growth pattern and include centrocyte-like cells. The expression of CD123, CD56, CD4, TCL1, CD2AP and CD303 helps with its correct classification [20].

Cutaneous reactive lymphoid hyperplasia may also mimic PCFL. In reactive hyperplasia, follicles show the typical outer mantle zone, encircling well polarized GC,
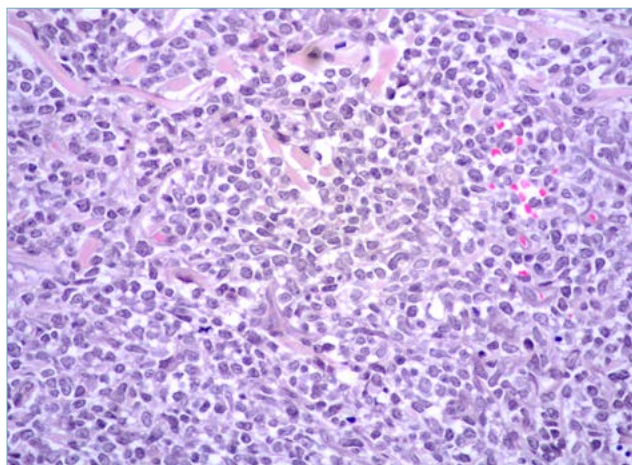
Figure 10. Skin. Blastic plasmacytoid dendriitic cell neoplasm. "Centrocyte-like" features of the neoplastic elements. HE, 400x.
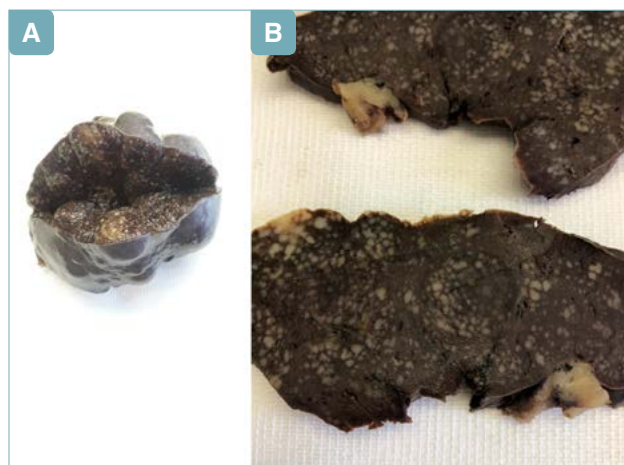

Figure 11. A Follicular lymphoma of the spleen, gross appearance. Courtesy of Dr. Marco Toraldo, Anatomia Patologica, Ospedale di Foligno; B Follicular lymphoma of the spleen, gross appearance. Courtesy of Dr. Marco Toraldo, Anatomia Patologica, Ospedale di Foligno.

as highlighted by Ki-67. Molecular studies (polymerase chain reaction - PCR) can help support PCFL diagnosis, examining immunoglobulin heavy-chain and light-chain genes and confirming clonality. The presence of clonality supports PCFL, if in the right clinicopathological context. However, pitfalls do exist. DNA may be of insufficient quality for molecular analysis, particularly in formalin-fixed, paraffin-embedded tissue. When DNA is of poor quality, false-negative results can occur [21]. PCFL may not have a detectable monoclonal population and false-negative results are possible [22]. In addition, when a B-cell population emerges as dominant clone in reactive lymphoid hyperplasia, false-positive results can occur [23].

Figure 12. A Follicular lymphoma of the spleen, follicular pattern of growth. HE, 100x; B Follicular lymphoma of the spleen. Numerous centrocytes and few centroblasts. HE, 400x.

Splenic FL

Primary splenic FL is very rare. To date, just a few studies on primary splenic FL have been performed [24]. Its macroscopic appearance with multiple, small nodules can resemble splenic marginal zone lymphoma (Fig. 11). Histologically, the spleen shows a micronodular pattern, GC cytology and frequent marginal zone-like cells at nodules periphery (Fig. 12). Mollejo et al. reported the clinicopathological features of primary splenic FL subdividing it in 2 groups: the first resembling classical FL with the presence of t(14;18) and CD10 expression, which is usually diagnosed at advanced stage; the second, characterized by high grading, elevated proliferation index and BCL2 negativity, more often restricted to the spleen (Fig. 13) [24]. Splenic FL shows some clinical features different from nodal FL. Hepatitis C virus (HCV)-positive status is significantly more common

in patients with splenic FL. Ann Arbor stage III or IV and high-risk FLIPI (Follicular Lymphoma International Prognostic Index) are less common in splenic FL. The progression-free survival is worse in patients undergoing splenectomy without postoperative chemotherapy. These results suggest the spleen itself, as primary lesion, might affect the biological characteristics of FL. Splenic FL should probably be considered a distinct type of FL compared to nodal FL [25].

Rare extranodal sites involved by FL

Rarely, FL may involve uncommon extranodal sites such as peripheral nerves, muscle, peritoneum, dura, pancreas, conjunctiva and orbit [26-33].

Figure 13. A Follicular lymphoma of the spleen. CD3-negative neoplastic elements, 100x; B Follicular lymphoma of the spleen. CD20-positive neoplastic elements, 100x; C Follicular lymphoma of the spleen. CD10-positive neoplastic elements, 100x; D Follicular lymphoma of the spleen. BCL6-positive neoplastic elements, 100x;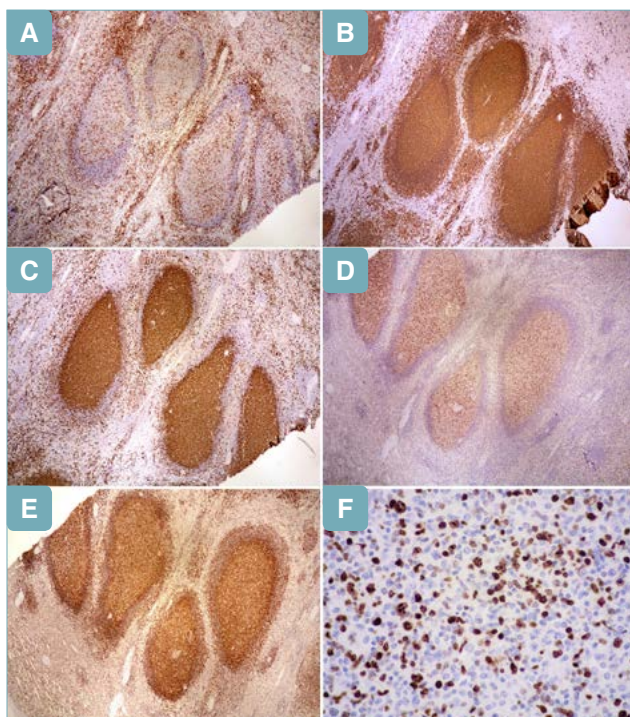 E Follicular lymphoma of the spleen. BCL2-positive neoplastic elements, 100x; F Follicular lymphoma of the spleen. Proliferative index of neoplastic elements (KI-67/MIB1 15-20%), 100x.

Unusual phenotypes and molecular pitfalls in FL

BCL2-negative FL. BCL2 protein expression varies from 85-90% in grade 1-2 to less than 50% in grade 3 FL. BCL2 expression is related to the recurrent translocation t(14,18)(q32;q21) involving IGH and BCL2. BCL2-negative FL are explained by either true absence of t(14;18) or by mutation in BCL2 epitope usually recognized by clone 124 anti-BCL2 antibody. In these cases of BCL2 "pseudo-negative" FL, neoplastic follicles are immunoreactive using different anti-BCL2 antibodies such as clones E17 and/or SP66 [34,35]. Thus, the absence of BCL2 should not be interpreted as evidence against FL diagnosis, if other features are consistent with FL. Furthermore, the use of additional clones of anti-BCL2 antibody in the work-up of BCL2-negative FL is advisable.

CD10/BCL6 negative FL. A subset of FL, more fre-

quently grade 3A, is CD10-negative and/or BCL6-negative. Recently, novel markers like Stathmin, GCET1, HGAL, and LMO2 have been introduced that can be useful in CD10 and/or BCL6-negative FL [36].

CD30 positive FL. A small percentage of FL, mostly grade 3, may contain sparse CD30-positive cells. This phenomenon is usually restricted to large centroblasts and/or to pleomorphic Hodgkin-Reed Sternberg (HRS)-like cells of grade 3 FL [37].

CD5 positive FL. CD5 is expressed by 5% of FL. CD5-positive FL can have the floral and/or diffuse patterns of growth. CD5 expression has been associated with higher International Prognostic Index (IPI), higher rate of transformation, and shorter progression-free survival [38].

IRF4/MUM1 positive FL. IRF4/MUM1 expression is detected in grade 3B FL as marker of late GC differentiation [39]. Low to moderate IRF4/MUM1 expression may be observed even in low-grade FL. High IRF4/MUM1 expression has been recently reported to be predictive of poor outcome in low-grade FL [40].

The t(14;18)(q32;q21)/IGH-BCL2 translocation is present in common FL, although its frequency varies greatly depending on FL grading. The translocation t(14;18) is detected in up to 90% of low-grade FL, but in only 60-70% of grade 3A and 15-30% of grade 3B FL [41]. Furthermore, BCL2 translocation variants such as t(2;18) and t(18;22) have been described. FL with BCL6 translocation represents 10-15% of cases, more frequently grade 3A and 3B. These FL strongly express BCL6, but are quite often BCL2 and/or CD10 negative [42].

The updated WHO classification recognizes the category of high-grade B-cell lymphoma (HGBCL) with MYC and BCL2 and/or BCL6 rearrangements, so called double-hit (DH) or triple-hit (TH) lymphomas [1]. Occasionally, "de novo" low-grade or grade 3 FL may carry MYC and BCL2 and/or BCL6 gene rearrangements, but should not be classified as HGBCL, unless undergoing a clear-cut transformation. The prognostic significance of concurrent MYC and BCL2 or BCL6 rearrangements in otherwise typical FL is an open question. Some studies report an aggressive course, but better response to more intensive regimens, while others show a behavior similar to FL lacking MYC rearrangement [43-45].

Elucidation of the clinicopathological features of NOTCH-mutant FL. NOTCH1 and NOTCH2 have been recently reported in several B cell lymphoma. The role of these mutations in FL is not known. A recent study identified NOTCH1 and NOTCH2 mutations in 6.3% of FL. NOTCH-mutated FL showed lower frequency of t(14;18), higher incidence of splenic involvement and female predominance. Furthermore, transforma-

tion was more frequently identified in NOTCH-mutated FL than in wild-type cases. These results indicate NOTCH mutations are uncommon in FL, but may occur in a subset of cases with distinctive features [46].

Grade 3B FL

The number of centroblasts is the key feature for FL grading. Grade 3B is a FL with a purely follicular growth pattern, composed only by centroblasts (Fig. 14). Pure 3B FL is rare and clinical data on this enigmatic entity remain scarce [39]. Most 3B FLs focally contain diffuse areas, therefore, deserving the diagnosis of DLBCL [47]. Furthermore, grade 3B rarely coexists with grade 1-2 or 3A, suggesting a divergent pathogenesis [48]. Grade 3B FL is generally CD10-negative and IRF4/MUM1-positive (Fig. 15). The translocation t(14;18)(q32;q21) juxtaposing the IGH and BCL2 genes is rare in pure 3B FL (13%), despite expressing BCL2 protein in 69% of cases. BCL6 rearrangement occurs rarely in pure 3B FL, whereas increased TP53 expression is rather common (31%). Grade 3B FL is still an evolving subclass. Physicians should understand its aggressive nature, requiring timely attention, compared with grade 3A. In many aspects 3B FL resembles de novo DLBCL. Some studies suggest it may represent a morphological variant of DLBCL with a follicular pattern of growth [39]. Histology, immunophenotypic profile and chromosomal aberrations of pure 3B FL resemble DLBCL, particularly non-GCB type. It is widely accepted 3B FL is distinct from other types of FL and it is intriguing to speculate it may represent a follicular growing variant of DLBCL.
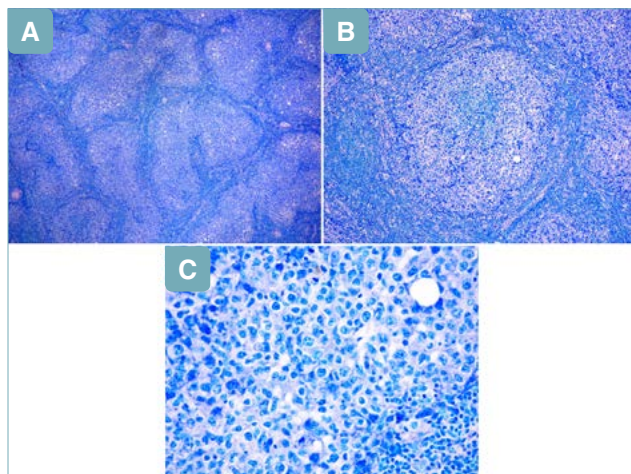

Figure 15. A Lymph node. Follicular lymphoma 3B. CD20 immunostaining, 40x; B Lymph node. Follicular lymphoma 3B. CD10 immunostaining, 200x; C Lymph node. Follicular lymphoma 3B. BCL6 immunostaining, 200x; D Lymph node. Follicular lymphoma 3B. BCL2 immunostaining, 400x; E Lymph node. Follicular lymphoma 3B. LMO2 immunostaining, 100x; F Lymph node. Follicular lymphoma 3B. KI-67/MIB1 immunostaining, 100x.

Figure 14. A Lymph node. Follicular lymphoma 3B. Giemsa, 40x; B Lymph node. Follicular lymphoma 3B. Giemsa, 100x; C Lymph node. Follicular lymphoma 3B. Giemsa, 400x.
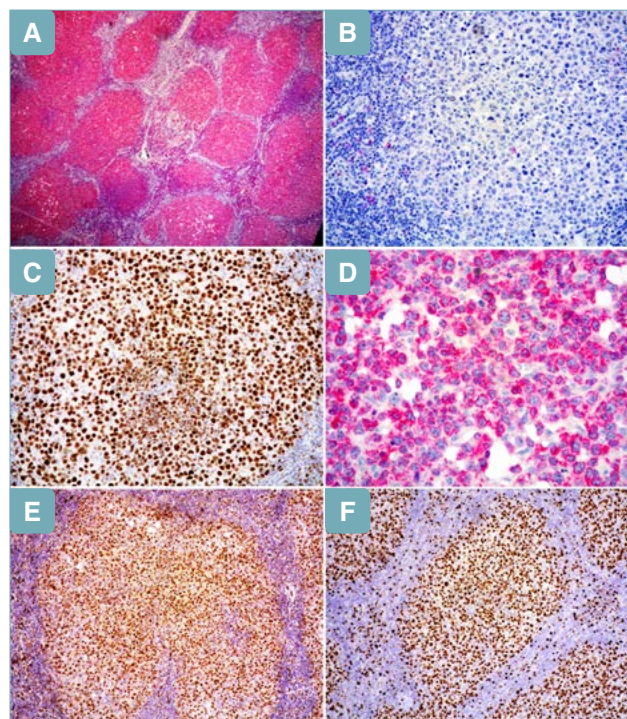
Transformation of nodal FL

It is well recognized that clinical aggressiveness and risk of transformation to DLBCL increase proportionally to the number of centroblasts and proliferative fraction. Transformation or progression occurs in 30% of FL. The current WHO criteria for transformed FL include a diffuse pattern of growth with centroblasts > 15/HPF (grade 3) [1]. In other words, the presence of grade 3 cytology in a diffuse pattern constitutes a DLBCL.

Currently, transformed FL is classified as DLBCL, or high-grade B-cell lymphoma (HGBCL) with MYC, BCL2 and/or BCL6 rearrangements or HGBCL not otherwise specified (in absence of MYC, BCL2 and/or BCL6 rearrangements). The HGBCL category has variable morphology, including DLBCL, Burkitt lymphoma, and/or "blastoid" morphology. "Burkitt-like" cases are reminiscent of both DLBCL and Burkitt lymphoma, not fulfilling diagnostic criteria for either entity.

Cases with so-called "blastoid morphology" show diffuse cohesive sheets of monotonous, small to medium-sized cells, high proliferation index, and starry-sky pattern. The cells have round nuclei with finely dispersed chromatin, inconspicuous nucleoli and a small rim of cytoplasm. These cells resemble lymphoblasts or the blastoid variant of MCL. Staining for TdT, Cyclin D1 and SOX11 should be performed.

More rarely, FL may transform into Hodgkin lymphoma, plasmablastic lymphoma, histiocytic sarcoma (HS) or precursor B cell lymphoblastic leukemia/lymphoma [49-52].

Lymphoblastic-type transformation of FL is a rare event with a poor outcome. It has to be differentiated from "de novo" FL with blastoid features, which has the typical FL phenotype and genetic abnormalities, without TdT expression. To avoid any confusion, the current WHO classification recommends the term "transformed FL of lymphoblastic type, TdT positive".

Recent studies suggested that transformation might occur in early neoplastic progenitors rather than in later subclones [53]. Thus, the phenomenon of transformation could be explained by a divergent evolution from a common precursor which was the founder cell of initial FL, and then evolved into DLBCL, histiocyte sarcoma, or lymphoblastic B-cell neoplasia [54].

Clonality studies are useful; matching rearrangements between initial FL and subsequent high grade lymphoma confirm a clonal relationship.

Composite FL

Composite lymphoma (CL) represents a fascinating process. It consists of two or more morphologically and immunophenotypically distinct lymphomas within the same anatomic site [55,56]. Its incidence ranges from 1 to 4.7% of total lymphomas, although CL may be more common than previously thought [57,58]. CL can arise synchronously or metachronously and can be clonally related or not. Regardless of the distinctive histology of the different components, in some cases the components are clonally related, whereas in others they are clonally unrelated, representing the "collision" of clonally unrelated tumors. With the advent of molecular analysis, it became clear that, in a subset of cases, CL components share a common clonal origin, suggesting derivation from a common precursor cell [59,60].

An adequate sampling is required to establish CL diagnosis. CL can be composed of FL and MCL, FL and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), FL and nodal marginal zone lymphoma (NMZL), FL and nodular lymphocyte predominance Hodgkin lymphoma (NLPHL), FL and classic Hodgkin lymphoma (CHL). Cases of FL associated with DLBCL, HGBCL, Burkitt lymphoma and B-lymphoblastic lymphoma/leukemia have to be excluded, because they represent high-grade transformation.

CL with FL and MCL have been rarely reported. FL component is typically low-grade, BCL2 positive and harbors the t(14;18) translocation. The MCL component shows a diffuse or in situ mantle-zone growth pattern, it is CCND1 positive and harbors the t(11;14) translocation [61]. Morphologically, the nodal architecture is intact and reactive follicles are mainly distributed in the cortex. The mantle zone is preserved and CCND1 positive cells are often restricted to the mantle zone [62]. Some studies suggest FL and MCL are clonally related, originating from the same preneoplastic clone [59,63,64].

CL with FL and CLL/SLL is extremely rare (Fig. 16) [65]. An interesting study of Boiocchi et al. supported the notion that composite low-grade B-cell lymphomas are usually biclonal [66]. Another recent study, reporting the largest case series of composite CLL/SLL and FL did not perform microdissection, so that the relationship between the two components cannot be definitively determined [65].

Recent examples of composite FL and NMZL, studied by PCR sequencing of IGH from microdissected NMZL and FL components, showed different sequences in the CDR3 region, suggesting the presence of two different clones [67].

Rarely, composite FL and NLPHL have been described, but the clonal relationship was not established, due to insufficient tissue for laser capture microdissection [68,69]. Composite CHL and FL have been reported, in some of which the CHL and FL components were clonally related. CHL may display the translocation t(14;18), suggesting a common origin (common B-cell precursor) of CHL and FL components. In a series of 19 composite cases involving CHL and other non-Hodgkin lymphomas, a shared clonality was demonstrated in 12/19 (63%) cases [58,70,71].

T-cell lymphoma associated with low-grade B-cell lymphoma is very rare. A composite FL and T-cell lymphoma is rarely reported [72,73]. The genomic aberration may have occurred in an early lymphoid progenitor which underwent divergent evolution via additional genomic alterations, resulting in heterogeneous subclones and eventually T-cell and B-cell neoplasms [72].

Occasionally, small innocuous aggregates of Langherans cells are identified within FL. Histiocytic and Langherans cell neoplasms occurring synchronously or sequentially in FL patients have been reported. FL and Langherans cell neoplasms or histiocytic sarcoma often share a common cell precursor (clonally related) [51,74].
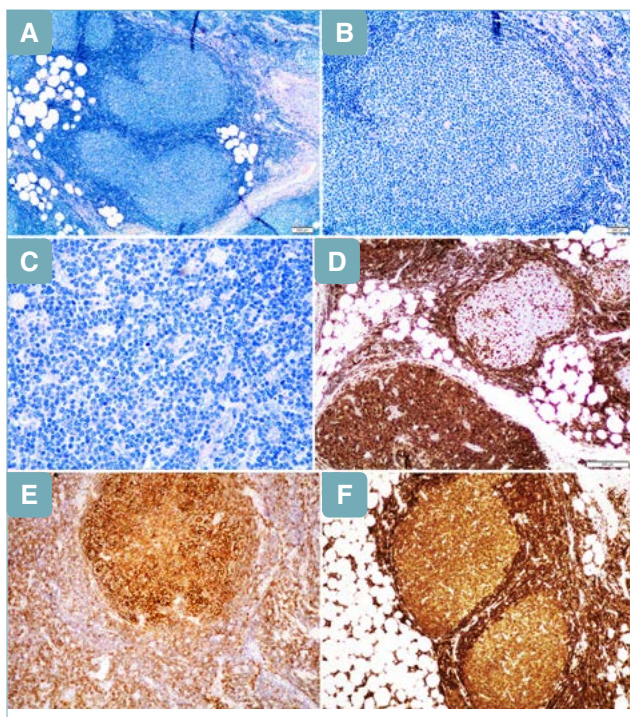
Figure 16. A Lymph node. Composite lymphoma: Follicular lymphoma and small lymphocytic lymphoma/chronic lymphocytic leukaemia. Giemsa, 100x; B Lymph node. Composite lymphoma: Follicular lymphoma and small lymphocytic lymphoma/chronic lymphocytic leukaemia. Giemsa, 200x; C Lymph node. Composite lymphoma: Follicular lymphoma and small lymphocytic lymphoma/chronic lymphocytic leukaemia. Giemsa, 400x; D Lymph node. Composite lymphoma: Follicular lymphoma and small lymphocytic lymphoma/chronic lymphocytic leukaemia. CD5 immunostaining. 100x; E Lymph node. Composite lymphoma: Follicular lymphoma and small lymphocytic lymphoma/chronic lymphocytic leukaemia. CD23 immunostaining. 100x; F Lymph node. Composite lymphoma: Follicular lymphoma and small lymphocytic lymphoma/chronic lymphocytic leukaemia. BCL2 immunostaining. 100x.

CL diagnosis is challenging, requiring careful interpretation of morphology, immunohistochemistry and fluorescence in situ hybridization (FISH) analysis as well as flow cytometry, particularly when both components show identical immunoglobulin light chain restrictions and/or overlapping immunophenotypic features. A handful of CL have been reported, few of which have been characterized in terms of clonal relationships. IGH gene rearrangement analysis is critical to demonstrate the clonal relationship. It is recommended to use not only morphology, immunohistochemistry and FISH, but also PCR or next-generation

sequencing (NGS) of the IGH and T-cell receptor gene rearrangements. Molecular studies are proving to be invaluable in CL workup. FISH, immunoglobulin rearrangement and sequencing as well as NGS technology can be improved by tissue microdissection. IGH analysis on whole tissue sections may not be helpful and laser capture microdissection is necessary to purify, or enrich individual components, in order to allow an interpretable gene rearrangement analysis. Thus, the power of microdissection coupled with molecular analysis needs to be considered. Recently, the concept is emerging that CL may represent different phenotypes of an identical shared common progenitor [71]. The analysis of additional CL cases is necessary to further investigate the clonal relationship between the individual components and to get better insights into CL pathogenesis.

Bone marrow involvement by FL

Usually, bone marrow trephine biopsy is performed for FL staging. Bone marrow involvement is quite common, occurring in 80% of FL patients. Typically, lymphoma is aligned along the trabecular bone (paratrabecular pattern), although interstitial and/or nodular patterns may be seen (Fig. 17). Rarely, bone marrow is extensively involved by FL (Fig. 18) [75]. Grading is not recommended on bone marrow biopsy. In absence of previous rituximab therapy, CD20 is sufficient to reveal even subtle bone marrow infiltration, whereas CD10
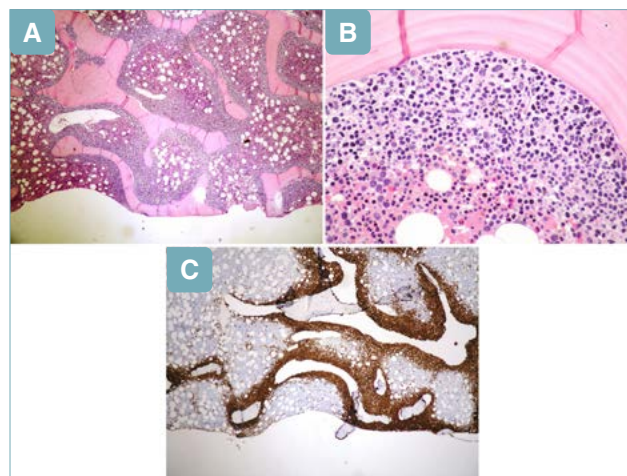

Figure 17. A Bone marrow. Follicular lymphoma, paratrabecular pattern of growth. HE, 100x; B Bone marrow. Follicular lymphoma, paratrabecular pattern of growth. HE, 400x; C Bone marrow. Follicular lymphoma, paratrabecular pattern of growth. CD20 immunostaining, 100x.
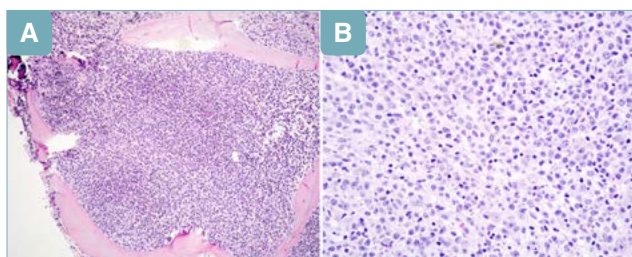
Figure 18. A Bone marrow. Follicular lymphoma, diffuse pattern of growth. HE, 100x; B Bone marrow. Follicular lymphoma, diffuse pattern of growth. HE, 200x.

and BCL6 are typically downregulated or may be totally negative. BCL2 staining is not useful, and does not add any further information. Furthermore, BCL2 is expressed by many other indolent low-grade B-cell lymphomas. Sometimes, a nodal transformed DLBCL coexists with low-grade FL in bone marrow, representing the so-called "discordant" lymphoma [76].

Approach to histopathological diagnosis of FL by core needle biopsy

Correct lymphoma classification is the best way to obtain relevant information for treatment and outcomes. The criteria for FL diagnosis and, by extension, the most appropriate therapeutic strategies are based largely on histologic evaluation of surgically excised specimens. Nonetheless, recently, an increasing reliance on core needle biopsy (CNB) of lymph nodes is evident. In many institutions, CNB is the primary diagnostic procedure in the suspect of lymphoma. Several studies on the effectiveness of CNB suggested that CNB yields an adequate diagnosis for treatment decision in about 65% to 75% of cases [77-80].

The reasons of the increasing popularity of this procedure are briefly summarized below. One of the most important considerations leading to CNB over excisional biopsy is urgency. However, in 25% of cases, CNB fails to yield an actionable diagnosis, further delaying therapy (Tab. I).

Since CNB can give only partial information, excisional biopsy of the lymph node should be performed, whenever possible. CNB has limitations, which is not particularly surprising, given how critical the architectural pattern is in FL diagnosis (Tab. II). Histological pattern, grading, immunohistochemical interpretation, including proliferative index, as well as detection of areas of transformation are common dilemmas, as many samples do not contain the recommended 10 follicles. Accu-

Table I. Advantages of core needle biopsy.

1	Diagnostic urgency
2	Sparing surgical procedure to the patient [patient compliance]
3	Risk of complications minimized [little morbidity]
4	Lymph nodes difficult to be removed can be sampled [deep-seated lymph nodes]
5	75% less expensive than excisional lymph node biopsy [cost-effectiveness]
6	Excluding non-hematopoietic tumors
7	Staging patients with known lymphoma
8	Assessment for relapse of lymphoma [change in the histologic findings; transformation]

Table II. Disadvantages of core needle biopsy.

1	Small specimen size
2	Sampling error
3	Artifactual distortion of morphologic features
4	Adequacy of tissue for ancillary studies [exhaustion of the paraffin block]

rate grading may be very difficult on CNB. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology are quite explicit, regarding the preference of excisional biopsies at the time of initial diagnosis, whenever feasible [77,80,81]. Despite the evolution of diagnostic methodologies, the use of ancillary techniques only occasionally compensates the loss of diagnostic specificity due to limited sampling.

The current WHO classification states "accurate grading cannot be performed on fine-needle aspiration and may be difficult on core needle biopsy. Therefore, an excisional biopsy is recommended for primary diagnosis".

Conclusion

Under the broad heading of FL, diseases with different clinicopathological features are included. Diverse molecular pathways are probably associated with different clinical features and outcomes.

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