

Review Article

# Precursory or early lesions of follicular lymphoma: clinical features, pathology, and genetics

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Follicular lymphoma (FL) is an indolent B-cell lymphoma with a germinal center (GC) B cell phenotype that typically harbors t(14;18)(q32;q21). t(14;18) juxtaposes *IGH* on 14q32 and *BCL2* on 18q21, resulting in overexpression of the anti-apoptotic BCL2 protein. However, t(14;18) is also found in the peripheral blood or lymphoid nodes (LNs) of otherwise healthy individuals. Moreover, overt FL has several additional gene alterations involved in epigenetic modification, JAK/STAT signaling, immune modulation, and NF-κB signaling, indicating multi-step lymphomagenesis in FL. There are two early or precursory lesions of FL: t(14;18)-positive cells in the peripheral blood of otherwise healthy individuals and *in situ* follicular B-cell neoplasm (ISFN). t(14;18)-positive cells are found in 10%–50% of healthy populations, and their incidence and frequency increase with age. The detection of t(14;18) in peripheral blood is a predictive factor for an increased risk of overt FL development. In contrast, ISFN is a histopathologically recognizable precursory lesion, in which t(14;18)-positive cells are confined to the GC of otherwise reactive LNs. ISFN is usually detected incidentally, with an incidence ranging from 2.0% to 3.2%. Occasional ISFN cases have concurrent or metachronous clonally related overt FL or aggressive B-cell lymphoma of a GC phenotype. t(14;18)-positive cells in peripheral blood and isolated ISFN, by themselves, are asymptomatic with limited clinical significance; however, investigations of t(14;18)-positive precursory or early lesions offer meaningful insights into the pathogenesis of FL. This review summarizes the epidemiology, clinical features, pathology, and genetics of precursory or early lesions of FL.

**Keywords:** t(14;18), BCL2, follicular lymphoma, *in situ* follicular B-cell neoplasm

## INTRODUCTION

Follicular lymphoma (FL) is a common indolent B-cell lymphoma that exhibits an immunophenotype of germinal center (GC) B cells. In Japan, FL accounts for 13.5% of newly diagnosed cases of lymphoma.<sup>1</sup> Histopathologically, typical FL is characterized by predominantly nodular proliferation of centrocytic B cells.<sup>2</sup> In addition to pan-B cell markers (including CD20, CD19, and CD79a), GC B cell markers (CD10 and BCL6) are typically expressed in tumor cells.<sup>2</sup> A genetic hallmark of FL is a balanced translocation of chromosome 14q32 and 18q21, which is found in approximately 90% of FLs.<sup>2–4</sup> This t(14;18)(q32;q21) juxtaposes immunoglobulin heavy chain (*IGH*) gene enhancer on 14q32 and *BCL2* on 18q21, leading to the transcription upregulation of *BCL2*. As BCL2 is an anti-apoptotic protein, this *IGH::BCL2* gene rearrangement enables FL cells to resist apoptosis in GCs.<sup>4</sup> This crucial anti-apoptotic property facilitates the lymphomagenesis of FL. However, t(14;18) is not

infrequently detected in lymphocytes in peripheral blood and reactive lymph nodes (LNs) of otherwise healthy individuals.<sup>5</sup> In addition, recent molecular studies on FL identified a number of somatic mutations of genes involved in epigenetic modification (e.g., *KMT2D*, *CREBBP*, and *EZH2*), JAK/STAT signaling (*SOCS1* and *STAT6*), immune modulation (*B2M*, *CD58*, and *TNFRSF14*), and B cell receptor (BCR)–NF-κB signaling (*BCL10*, *CARD11*, and *CD79B*).<sup>4</sup> These findings suggest that lymphomagenesis of FL is a multi-step process.

Considering the multi-step pathogenesis of FL, some FL-like early or precursory lesions have been recognized. These FL-like lesions include t(14;18)-positive cells in peripheral blood and *in situ* follicular B-cell neoplasm (ISFN).<sup>6</sup> In these conditions, FL-like cells harboring t(14;18) are, most often incidentally, detected by molecular and/or histopathological examination. These neoplastic processes are confined to a certain anatomical component without systemic distribution or symptoms such as overt FL.


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This review discusses the epidemiological, clinicopathological, pathological, and genetic features of precursory or early lesions of FL.

### t(14;18)-POSITIVE CELLS IN PERIPHERAL BLOOD OF OTHERWISE HEALTHY INDIVIDUALS

t(14;18) translocation is due to erroneous VDJ recombination of the *IGH* gene in bone marrow at the pre-B cell stage,<sup>4,7</sup> and t(14;18)-positive B lymphocytes circulate in the peripheral blood or reactive lymphoid tissues of individuals without FL. These t(14;18)-positive B cells exist at very low frequency in peripheral blood approximately ranging from  $1 \times 10^{-6}$  to  $1 \times 10^{-2}$ , as quantified by quantitative PCR.<sup>5,8-15</sup> Of note, a study investigated the distribution of t(14;18)-positive cells with a cell sorter and showed that the positive cells are more enriched in IgM memory (median:  $380 \times 10^{-6}$ ) than in antigen-naïve (median:  $16 \times 10^{-6}$ ) or switched memory (median:  $5 \times 10^{-6}$ ) B cells.<sup>16</sup> This finding demonstrated that t(14;18) is generated during early B cell development in bone marrow and that affected cells may mature and expand in GCs.

Similar to other subclinical monoclonal proliferations, such as monoclonal gammopathy of undetermined significance (MGUS) and monoclonal B-cell lymphocytosis (MBL), t(14;18)-positive cells are not uncommon and are found in 10%–50% of otherwise healthy individuals by highly sensitive quantitative or nested PCR (Table 1). The reported incidence varies considerably according to the age and ethnicity of the individuals. Dölken *et al.* reported an age-dependent increase in the incidence of t(14;18)-positive

cells.<sup>9</sup> According to their study, young individuals aged less than 10 years had no t(14;18)-positive cells in their peripheral blood. In contrast, the prevalence of circulating t(14;18)-positive cells increased from the second to fifth decades of life, from 20% to 66%, and remained stable thereafter. In addition, the median frequency of circulating t(14;18)-positive cells showed an increase with age.<sup>9</sup> Hirt *et al.* also reported that t(14;18) frequency is positively associated with age but not with sex or smoking.<sup>12</sup> These findings suggest that the cumulative chance of erroneous VDJ recombination increases and that B cells with t(14;18) clonally expand during aging.

The incidence of overt FL may vary according to ethnicity. An earlier study by Chihara *et al.* showed that the population-based incidence of FL in Japan was significantly lower than that in the United States: the age-adapted FL incidence per 100 000 people in 2008 was 1.1 in Japan and 2.6 in the United States.<sup>1</sup> On the other hand, it is controversial whether the incidence of t(14;18)-positive cells in healthy individuals differs by ethnicity (Table 1). Yasukawa *et al.* investigated the incidence of t(14;18)-positive cells in Japan and Germany.<sup>11</sup> They reported that 16% (39/241) and 52% (39/75) of Japanese and German healthy individuals, respectively, harbor positive cells, suggesting a major reason for the difference in incidence of FL between Western countries and Japan.<sup>11</sup> In contrast, Levy *et al.* compared the incidences in Brazil by ethnic background. Interestingly, t(14;18) translocation in the peripheral blood was found in 53% (45/85) of white individuals, 79% (57/72) of black individuals, and 97% (68/70) of Japanese-descent.<sup>15</sup> Therefore, further validation is needed to determine whether the difference in the incidence of t(14;18)-positive cells in peripheral blood explains

**Table 1.** Incidences of t(14;18)-positive cells in peripheral blood and in situ follicular B-cell neoplasm (ISFN)

Study, year (reference)	Screening method	Country of origin	Sample (n)	Prevalence (%)
<b>t(14;18)-positive cells in peripheral blood</b>				
Roulland, 2014 (5)	qPCR	Europe	Total peripheral blood leukocytes (n=218)	29
Summers, 2001 (8)	qPCR	United Kingdom	Total peripheral blood leukocytes (n=481)	23
Dölken, 2008 (9)	qPCR	Germany	Mononuclear peripheral blood leukocytes (n=644)	45
Nambiar, 2010 (10)	Nested PCR	India	Mononuclear peripheral blood leukocytes (n=253)	34
Yasukawa, 2001 (11)	Nested PCR	Germany	Mononuclear peripheral blood leukocytes (n=75)	52
Yasukawa, 2001 (11)	Nested PCR	Japan	Mononuclear peripheral blood leukocytes (n=241)	16
Hirt, 2013 (12)	qPCR	Germany	Total peripheral blood leukocytes (n=3966)	39
Schmitt, 2006 (13)	Nested PCR	Germany	Total peripheral blood leukocytes (n=204)	24
Schmitt, 2006 (13)	qPCR	Germany	Total peripheral blood leukocytes (n=204)	19
Colon-Otero, 2017 (14)	Semi-nested PCR	USA, African American	Total peripheral blood leukocytes (n=77)	14
Colon-Otero, 2017 (14)	Semi-nested PCR	USA, White	Total peripheral blood leukocytes (n=167)	16
Levy, 2017 (15)	Nested PCR	Brazil, White	Mononuclear peripheral blood leukocytes (n=85)	53
Levy, 2017 (15)	Nested PCR	Brazil, Black	Mononuclear peripheral blood leukocytes (n=72)	79
Levy, 2017 (15)	Nested PCR	Brazil, Japanese-descent	Mononuclear peripheral blood leukocytes (n=70)	97
<b>in situ follicular B-cell neoplasm (ISFN)</b>				
Henopp, 2011 (29)	IHC (BCL2)	Germany	Lymph nodes (n=132)	2.3
Bermudez, 2016 (25)	IHC (CD10 and BCL2)	Spain	Lymph nodes (n=341)	3.2
Carvajal-Cuenca, 2012 (30)	IHC (BCL2)	Spain	Lymph nodes (n=100)	2.0
Oishi, 2022 (24)	IHC (BCL2)	Japan	Lymph nodes (n=340)	2.1

the different incidences of manifested FL across international populations.

Although t(14;18) constitutes the primary lymphomagenesis of FL, it is unclear whether healthy individuals harboring t(14;18)-positive cells have a higher risk of subsequent development of overt FL. Roulland *et al.* investigated t(14;18) in prediagnostic blood samples of healthy participants who developed FL after enrollment and those who did not (controls).<sup>5</sup> Notably the incidence of t(14;18) was significantly higher in FL participants (61.8%, 102/165) than in controls (33.0%, 115/346). In addition, the t(14;18) frequency—that is, the relative number of t(14;18)-positive cells in each individual—was significantly higher in participants who developed FL (median,  $1.8 \times 10^{-5}$ , range  $0.1\text{--}2130 \times 10^{-5}$ ) than in controls (median,  $0.2 \times 10^{-5}$ , range  $0.1\text{--}45.6 \times 10^{-5}$ ). There was demonstrated to be a 23-fold higher risk of subsequent FL in blood samples associated with a t(14;18) frequency  $> 10^{-4}$  (odds ratio, 23.17; 95% confidence interval, 9.98 to 67.3).<sup>5</sup> These risk estimates remained high and significant up to 15 years before diagnosis.<sup>5</sup> Collectively, although t(14;18)-positive cells are uncommonly detected in otherwise healthy individuals, especially in older individuals, high t(14;18) frequency seems to be a predictive biomarker for subsequent FL, effective years before diagnosis.

It has not been fully understood how t(14;18)-positive cells develop into early or precursory FL lesions. A possible key factor determining the development of FL includes the affinity of t(14;18)-positive cells to GC, as an  $\epsilon\mu$ -BCL2 mice model indicated that deregulated BCL2-expressing B cells recirculate as memory B cells and accumulate genetic abnormalities while they repeatedly pass through GCs.<sup>17</sup>

## ***in situ* FOLLICULAR B-CELL NEOPLASM (ISFN)**

### **Definition and terminology**

The 5<sup>th</sup> World Health Organization (WHO) classification defines ISFN as partial or complete colonization of some GCs by follicular B cells with *IGH::BCL2* and strong BCL2 expression in otherwise normal reactive LNs or lymphoid tissues at extranodal sites.<sup>6,18</sup> ISFN was first described as follicular lymphoma *in situ* (FLIS) by Cong *et al.* in 2002 and was subsequently defined more strictly by Jegalian *et al.* in 2011.<sup>19,20</sup> This entity was included as FLIS in the 4<sup>th</sup> WHO classification; however, given the limited clinical and prognostic impact, the term “neoplasia” rather than “lymphoma” was preferred.<sup>21</sup> Therefore, the revised 4<sup>th</sup> WHO classification defined *in situ* follicular neoplasia. Now, the 5<sup>th</sup> WHO classification slightly modified the terminology to *in situ* follicular “B-cell neoplasm” (ISFN).<sup>22</sup> The current WHO classification also notes that “*in situ* follicular neoplasia” is still acceptable, but that FLIS is not recommended.

### **Clinical features**

Similar to overt FL, ISFN usually affects middle-aged and older individuals, with a mean age in the 40s.<sup>6,18</sup>

Patients younger than 40 years old are rare, although an exceptional ISFN case of a 24-year-old man with a history of Crohn’s disease and autoimmune hepatitis has been reported.<sup>23</sup> Isolated ISFN (i.e., the pure form of ISFN without any overt lymphoma) is usually found incidentally in LNs resected for another reason or because of enlargement.<sup>18</sup> In a small number of cases, ISFN may be seen in GCs of secondary lymphoid follicles of extranodal organs. ISFN can involve more than one lymph node without progression to overt lymphoma; therefore, multiple lesions do not exclude the diagnosis of ISFN.<sup>24,25</sup> Individuals with isolated ISFN are usually asymptomatic and have excellent outcomes without developing overt FL, requiring no anti-lymphoma therapy.<sup>24–26</sup> If the lesion is precisely differentiated from FL, the progression of isolated ISFN is very low and at most 5%.

In contrast, some ISFN lesions are associated with concurrent or subsequent overt FL.<sup>27,28</sup> Cases of ISFN associated with non-FL lymphoma have also been reported.<sup>27</sup> Clonally-related ISFN and diffuse large B-cell lymphoma (DLBCL) lacking clinically manifested FL as an intermediate step have also been described.<sup>27</sup>

### **Epidemiology**

Because ISFN is most often an incidental finding in pathological examinations for other medical conditions, such as LN dissection for solid tumors, the exact incidence of ISFN is difficult to estimate. Four studies have investigated the incidence of isolated ISFN.<sup>24,25,29,30</sup> These studies examined LNs from individuals who underwent surgery, including lymphadenectomy for solid tumors or inflammatory conditions, using immunohistochemistry (Table 1). The reported incidence of isolated ISFN ranged from 2.0% (2 of 100) to 3.2% (11 of 341).<sup>24,25,29,30</sup> In Japan, a screening study using the BCL2 immunohistochemistry identified the incidence of ISFN to be 2.1% (7 of 340).<sup>24</sup> One caveat is that these screening studies mostly investigated LNs of relatively older individuals who underwent surgical treatment for solid cancers. Because B cells with t(14;18) are more prevalent in older individuals, the reported incidence of ISFN in otherwise healthy individuals could be potentially biased and may be higher than the actual incidence.

### **Histopathology**

ISFN is usually not detected by routine hematoxylin and eosin staining, and immunohistochemistry is required for its detection. The LN or extranodal lymphoid tissue involved by ISFN appears otherwise normal or reactive, exhibiting lymphoid hyperplasia with secondary lymphoid follicles.<sup>6,18,31</sup> The GCs with ISFN involvement may appear somewhat monotonous, lacking the tingible body macrophages and polarization seen in normal GCs (Figure 1); however, it is challenging to confirm the presence of ISFN without immunohistochemistry. Therefore, immunohistochemistry (especially for CD10 and BCL2) is essential for confirming ISFN.

The immunophenotype of ISFN is basically identical to that of classic FL (Figure 1). Neoplastic cells are positive for pan-B cell markers (i.e., CD19, CD20, CD79a, and



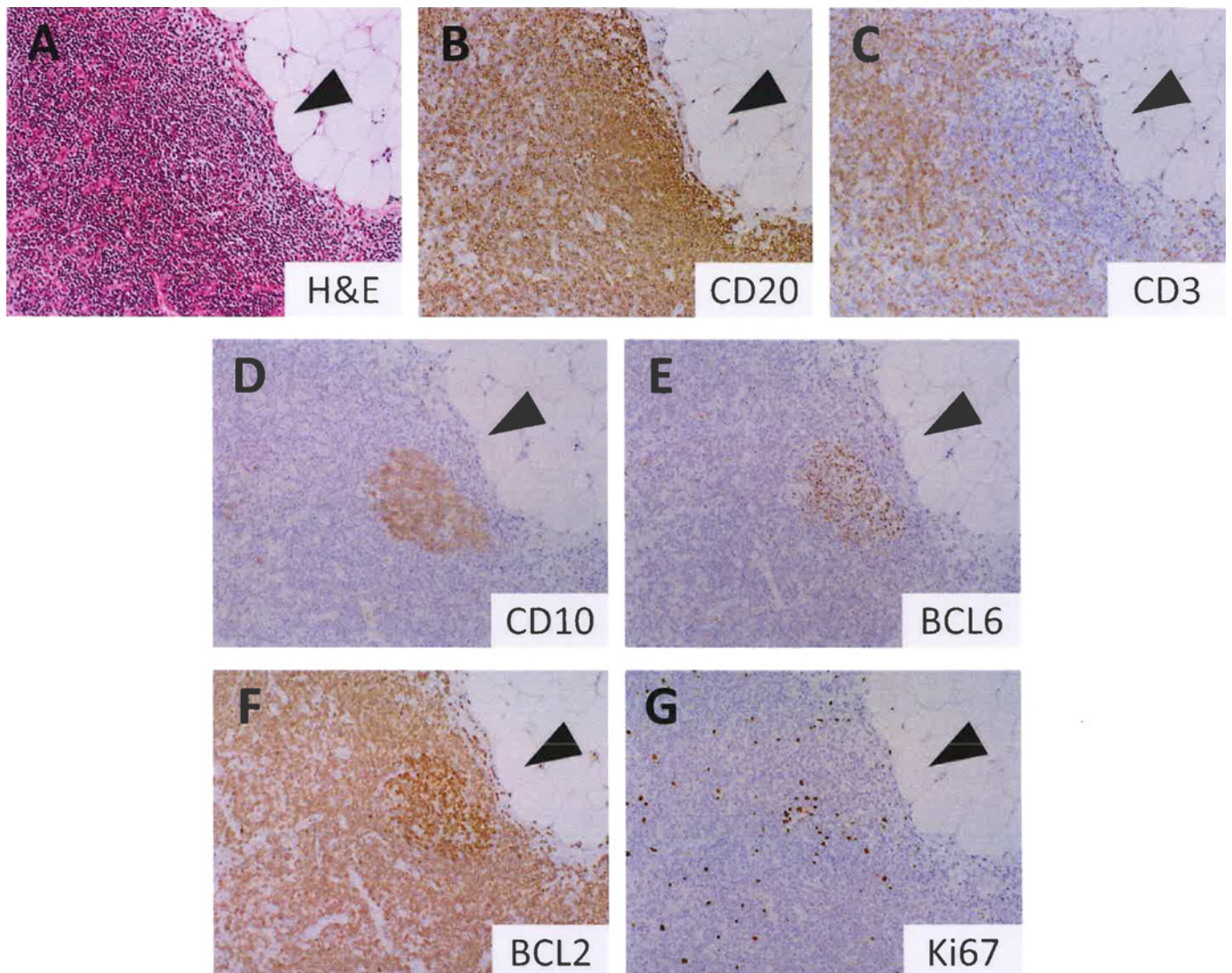
PAX5) and GC B cell markers such as CD10 and BCL6. As t(14;18) generates *IGH::BCL2* leading to the transcriptional upregulation of *BCL2*, neoplastic ISFN cells express the BCL2 protein.<sup>18,29</sup> This gene rearrangement can be confirmed at the DNA level by fluorescence *in situ* hybridization (FISH). Immunohistochemical analysis reveals that ISFN cells exhibit more intense BCL2 positivity than other BCL2-positive non-GC cells, and even classic FL with t(14;18).<sup>24,29</sup> This intense expression of BCL2 is a diagnostic hallmark of ISFN. The Ki67 labeling index is typically low. Neoplastic GCs contain a meshwork of follicular dendritic cells (FDCs) in the background, which is best highlighted by immunohistochemical staining for CD21 and/or CD23. Notably, the population of neoplastic ISFN cells varies by GCs: some GCs contain confluent BCL2-positive GC B cells, while others have scattered B cells strongly expressing BCL2 (Figure 2 and Figure 3).

An important difference in the immunophenotype of

ISFN and classic FL is the expression of activation-induced cytidine deaminase (AID). AID expression is a hallmark of GC reactions and at least a subset of classic FLs express AID. In contrast, Goyal *et al.* demonstrated that ISFN is negative for AID.<sup>32</sup> A lack of AID expression was also noted in duodenal-type FL,<sup>33</sup> an extremely indolent form of FL. As additional genetic abnormalities in FL cells are presumably triggered by AID, resulting in genomic instability, it is interesting that both low-risk FL variants, ISFN and duodenal-type FL, lack AID expression.

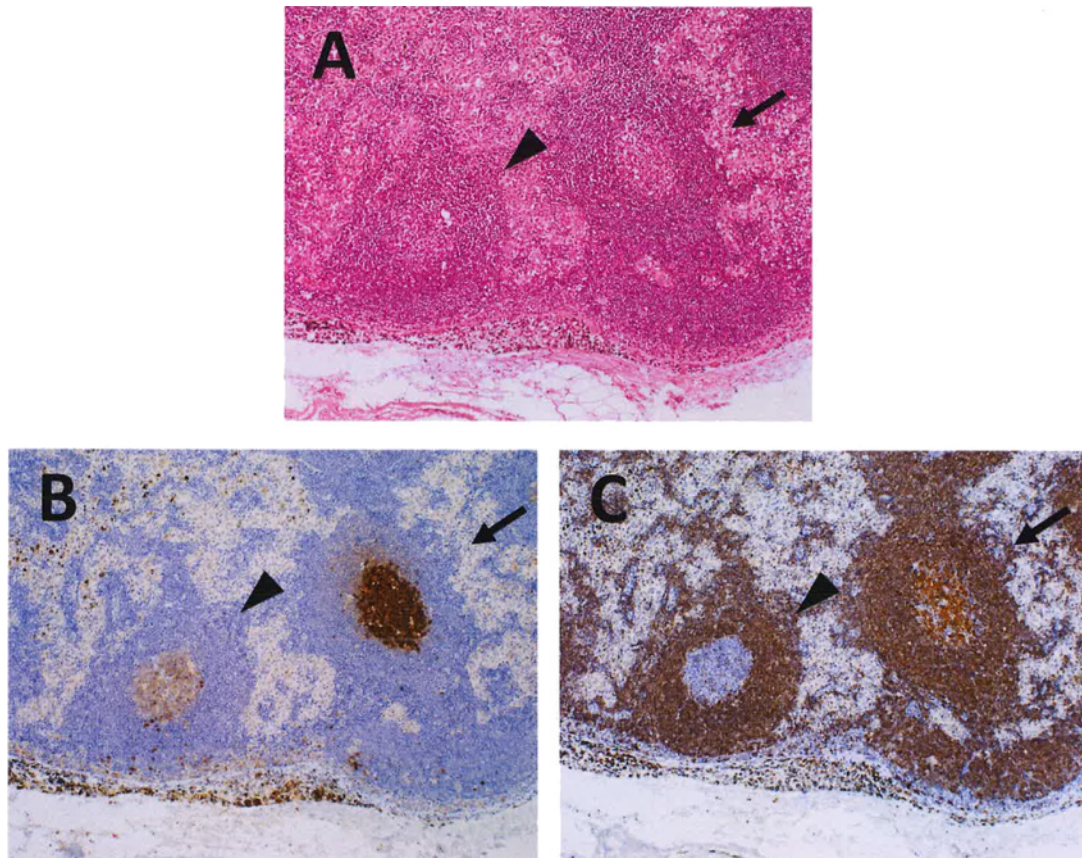
#### Differential diagnosis

Pure ISFN has limited clinical significance with very low risk to transform into overt FL. Therefore, in routine clinical practice, it is unnecessary to perform immunohistochemical screening for BCL2 ( $\pm$  CD10) in every reactive-looking LN for the purpose of excluding ISFN. Nonetheless, ISFN should be precisely differentiated from reactive follicular

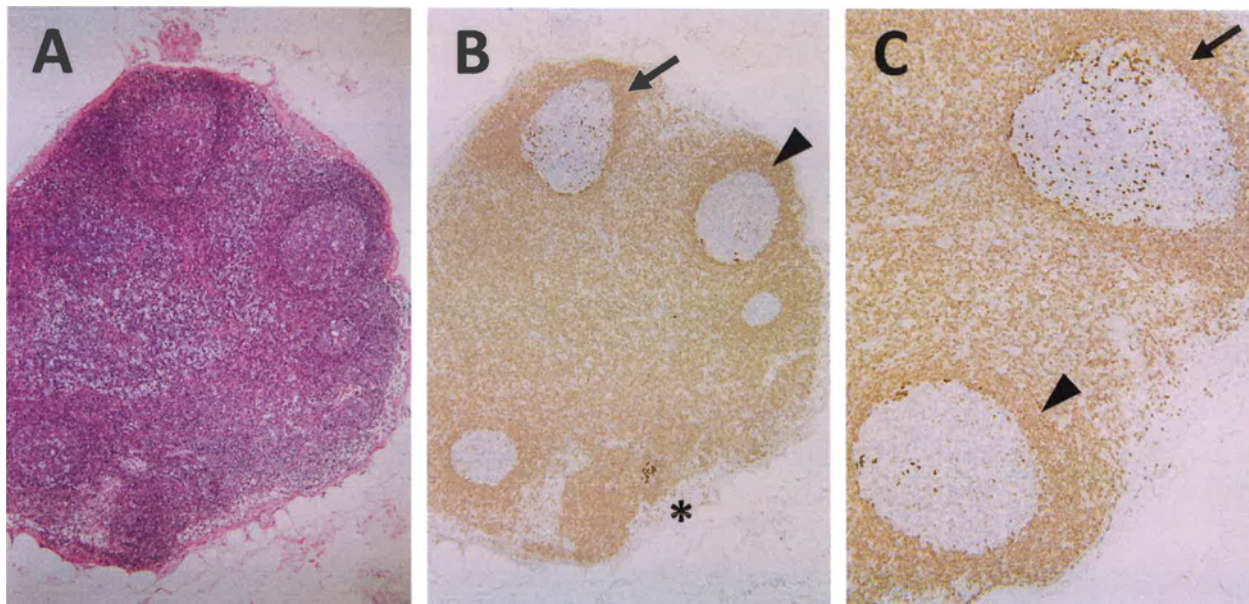


**Fig. 1.** Histopathology of isolated *in situ* follicular B-cell neoplasm (ISFN). Hematoxylin and eosin staining showing a lymphoid follicle with a monotonous germinal center (GC) (A). GC is involved by ISFN, in which neoplastic B cells are CD20<sup>+</sup> (B), CD3<sup>-</sup> (C), CD10<sup>+</sup> (D), BCL6<sup>+</sup> (E), and BCL2<sup>+</sup> (F). The ISFN lesion exhibits more intense BCL2 staining than the background B and T cells. The Ki67-labeling index is low (G).





**Fig. 2.** ISFN and a reactive GC. This example shows an ISFN (right, arrow) situated adjacent to a reactive GC (left, arrowhead) (A). ISFN exhibits co-expression of CD10 and BCL2.



**Fig. 3.** GCs variably involved by ISFN. (A) Hematoxylin and eosin staining demonstrates reactive-looking GCs. (B and C) Immunohistochemistry for BCL2 highlights a clear ISFN lesion (\*) and GCs with scattered ISFN cells strongly expressing BCL2 (arrow and arrowhead). Note that the number of BCL2-positive cells in GCs are variable as indicated by the arrow and arrowhead.

hyperplasia, FL, and partial involvement by FL (PFL). The distinction between reactive follicular hyperplasia and ISFN is usually straightforward, as GCs in reactive secondary lymphoid follicles are positive for CD10 and BCL6 but negative for BCL2. Primary lymphoid follicles consist of BCL2-positive B lymphocytes, potentially mimicking ISFN; however, B cells in primary lymphoid follicles are negative for GC markers such as CD10 and BCL6.

Differentiating FL from ISFN is clinically important. In classic FL, normal LN architecture is effaced by nodular/follicular or partially diffuse proliferation of neoplastic B cells co-expressing CD10 and BCL2. The neoplastic follicles in FL show so-called “back-to-back” arrangement, effacing normal structures of LNs. In contrast, ISFN preserved the follicular architecture of LNs with intact interfollicular areas and the medulla, mimicking reactive follicular hyperplasia.

The distinction between PFL and ISFN can be more challenging and is critically important because the former has a higher risk of progression to clinically significant FL.<sup>20</sup> An earlier study reported that approximately half of all patients with untreated PFL developed overt FL in a 14-year follow-up period. PFL is histopathologically distinct from ISFN in that it exhibits focal architectural alterations in the lymphoid follicles. Neoplastic follicles of FL are often larger than those of ISFN, and their margins may be ill-defined with attenuated mantle zones. Neoplastic GCs in the PFL are typically monotonous and consist mostly of centrocytes, although centroblasts are occasionally present. In contrast to ISFN, in which CD10 and BCL2 are strongly expressed, PFL exhibits more variable and often less intense CD10 and BCL2 expression. In addition, neoplastic B cells may show interfollicular distribution in the PFL. Genetically, an array comparative genomic hybridization (aCGH) study identified significantly more genomic alterations per sample in PFL than in ISFN.<sup>34</sup> Thus, given these clinical, pathological, and genetic data, partial involvement of FL is at a stage closer to overt FL than ISFN.

### Molecular Pathogenesis

Since the pathogenesis of FL is a multi-step process with a number of genetic abnormalities other than t(14;18),<sup>4</sup> it is crucial to understand the genetic features of ISFN, the histologically recognizable first step of FL lymphomagenesis. Genetic analysis of ISFN is technically challenging because neoplastic t(14;18)-positive cells are confined to GCs, requiring microdissection to obtain sufficient DNA from neoplastic cells.

Previous studies have investigated copy number alterations (CNAs) in ISFN using aCGH. According to Schmidt *et al.*, CNAs were rare in ISFN and, when present, ISFNs had fewer CNAs per sample than overt FL.<sup>34</sup> CNAs in paired samples of ISFN and overt FL were also studied. ISFN components showed no CNAs in five of the six cases. In contrast, Mamessier *et al.* examined CNAs in ISFNs (n=4) and found that all had chromosomal imbalances, although the number and length of CNAs in ISFN were smaller than those in overt FL.<sup>35</sup> Hence, both studies indicated that ISFN

shows less genomic complexity than overt FL and may represent an earlier lesion in the clonal evolution pathway of these lesions.

Some studies have investigated gene alterations in ISFN using next-generation sequencing (NGS). A Japanese study examined gene mutations in isolated ISFN cases (n=5) and found that ISFN had a few variants in FL-associated genes with varying but relatively low variant allele frequencies (VAFs). While variants in *HIST1H1E* (2/5), *KMT2D* (1/5), *ARID1A* (2/5), *BCL7A* (1/5), *CREBBP* (1/5), and *TNFRSF14* (1/5) were identified, no isolated ISFNs harbored *EZH2* Y646, one of the most frequently affected genes in overt FL.<sup>24</sup> In contrast, Schmidt *et al.* performed targeted sequencing on ISFNs paired with overt FL (n=6) and isolated ISFNs (n=5). They found frequent *CREBBP* mutations in ISFNs paired with overt FL (83%, 5/6), but only in one of five cases with isolated ISFN (20%, 1/5).<sup>28</sup> This finding suggests that *CREBBP* mutations are possibly early driver mutations that facilitate the acquisition of additional mutations and clonal evolution. These mutation profiling studies also imply that the molecular heterogeneity of isolated ISFNs, pure ISFNs, and ISFNs found in association with overt FL could be genetically distinct.

The clonal association between ISFN and associated aggressive B-cell lymphoma was investigated by Vogelsberg *et al.*<sup>27</sup> They collected ten paired cases of ISFN and DLBCL or high-grade B-cell lymphoma (HGBCL), and investigated their clonal evolution using microdissection and NGS. As expected, all ten patients exhibited a clonal relationship between ISFN and aggressive B-cell lymphoma, which was confirmed by immunoglobulin and/or BCL2 rearrangements and/or shared somatic mutations. Consistent with the results of their previous study, *CREBBP*, *KMT2D*, *EZH2*, *TNFRSF14*, and *BCL2* mutations were detected in ISFN. Notably, two clonal evolutionary patterns were observed (Figure 4). Eighty percent (8/10) of cases showed “branched” evolution, in which aggressive B-cell lymphoma, ISFN, and, when present, FL showed divergent evolution from a common progenitor. In contrast, a small number of cases (20%, 2/10) showed “linear” evolution with sequential stratification of mutations.

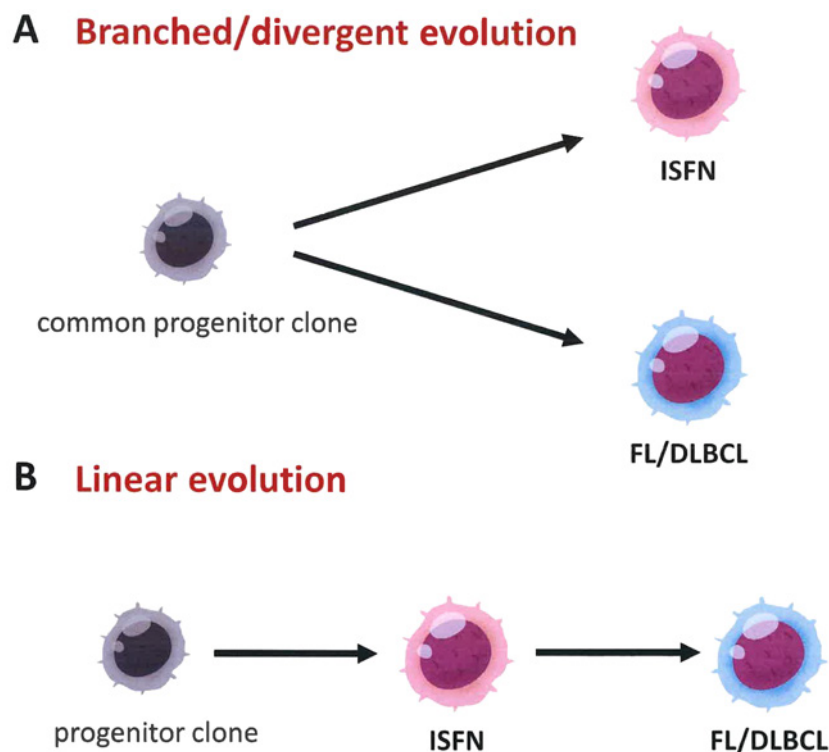
### CONCLUSIVE REMARKS

Although early or precursory lesions of FL, including t(14;18)-positive cells in peripheral blood and ISFNs, have limited clinical significance when identified, careful pathologic and molecular studies offer meaningful insights into the lymphomagenesis and progression of FL. In clinical practice, it is essential for both pathologists and clinicians to recognize the clinical relevance of these early lesions and share information concerning disease distribution in patients.

### CONFLICT OF INTEREST

The author has no conflicts of interest directly relevant to the content of this article.





**Fig. 4.** Two progression models for the generation of ISFN and overt B-cell lymphomas with a GC B cell phenotype. **(A)** In the branched or divergent evolution model, each ISFN and follicular lymphoma (FL) or DLBCL arises divergently from a shared progenitor clone harboring t(14;18). **(B)** In contrast, in the linear model, FL/DLBCL evolves directly from ISFN acquiring additional gene alterations.

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