








Review

B Lymphoproliferative Neoplasms of Uncertain Biological Significance: Report from the IV Workshop of the Italian Group of Hematopathology and Review of the Literature

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Abstract: Lymphoproliferative neoplasms of uncertain biological significance are increasingly encountered due to widespread usage of immunophenotypic and molecular techniques. Considering that clearer biological criteria and patient management have been established for B-cell lymphoproliferative diseases of undetermined significance occurring in the peripheral blood, many issues are still obscure for early lesions detected in lymphoid tissues. Regardless that some categories of lymphoproliferative neoplasms of uncertain biological significance have been recognized by the 4th edition of the WHO, other anecdotal early lymphoproliferative lesions still remain fully undefined. Some early lesions frequently originate from the germinal center, including atypical germinal centers BCL2-negative, an early pattern of large B-cell lymphoma with *IRF4* rearrangement, and “in situ” high-grade B lymphomas. Moreover, other early lymphoproliferative lesions arise outside the germinal center and include those developing within the setting of monocytoid B-cell hyperplasia, but they also can be directly or indirectly associated with chronic inflammations. This review aims to summarize the concepts discussed during the IV Workshop organized by the Italian Group of Hematopathology, focus on the state-of-the-art on B-cell lymphoproliferative neoplasms of uncertain biological significance, and offer operative insights to pathologists and clinicians in routine diagnostics.

Keywords: lymphoproliferative neoplasms of uncertain biological significance; monoclonal B-cell lymphocytosis; “in situ” follicular neoplasia; “in situ” mantle cell neoplasia; atypical germinal centers; large B-cell lymphoma with *IRF4* rearrangement; “in situ” high-grade B lymphomas; non-Hodgkin lymphoma; Hodgkin lymphoma

1. Introduction

The IV Workshop, organized by the Italian Group of Hematopathology, focused on lymphoproliferative neoplasms of uncertain biological significance. The long-standing concept of in situ/early neoplasia has been already established in epithelial tumors; the same approach is not so readily applicable to lymphoid proliferative disorders, due to the fact that lymphocytes are usually circulating and not sessile cells. Indeed, in this context, early lesions are often an incidental finding that partially/minimally involve an otherwise reactive-appearing lymph node and never progress in most instances. Along with the historical recognition of monoclonal immunoglobulins in the serum, namely monoclonal gammopathy of undetermined significance (MGUS), a clear conceptual definition of peripheral blood B-cell lymphoproliferative diseases of undetermined significance (monoclonal B-cell lymphocytosis) is well-established [1]. A series of early lesions histologically detected in lymphoid tissues, also in view of their uncertain risk of progression, are actually still seeking a biological determination. The early lesions within the lymphoid tissue accepted by the 4th edition of the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues are “in situ” follicular neoplasia and “in situ” mantle cell neoplasia [2] that could actually be considered as the tissue counterpart of circulating elements with t(14;18) and t(11;14) rearrangements (Table 1). “In situ” follicular neoplasia (ISFN) is defined as partial or total colonization of germinal centers by clonal B cells carrying the *BCL2* translocation characteristic of follicular lymphoma (FL) in a lymph node where the overall architecture is preserved [3,4]. ISFN is characterized by lack of polarization, closely packed centrocytes with very few, if present, centroblasts, although it is not commonly recognizable in routine H&E-stained sections [3]; this condition is frequently identified by an intense immunoreactivity for germinal center markers (e.g., CD10) and aberrant positivity for *BCL2*, along with a low proliferation index. ISFN must be distinguished from partial involvement by follicular lymphoma (pFL), where an architectural distortion is observed. The risk of progression of ISFN is very low (<5%) [5], and it does not seem to be influenced by the number of follicles involved within a single lymph node [5,6]. “In situ” mantle cell neoplasia (ISMCN) is defined as the occurrence of Cyclin D1-expressing B cells in nonexpanded mantle zones of otherwise morphologically reactive-appearing lymph nodes [4,7,8]. The clinical outcome has not been completely clarified; the progression into an overt mantle cell lymphoma (MCL) is uncommon [7], although ISMCN or minimal accumulations of Cyclin D1-positive B cells can sometimes be detected several years before developing an overt MCL [9]; additionally, it has been reported that ISMCN with expression of *SOX11* has a higher chance to progress [7].

In cases of ISFN and ISMCN, it is necessary to proceed to a complete staging workup to exclude an overt lymphoma in another site. Additionally, a composite form, namely ISFN and ISMCN, can be associated with another overt lymphoma, as presented in the first three cases of the Workshop.

Other anecdotal early lymphoproliferative lesions with uncertain biological significance have been previously published and are not present in the 4th edition of the WHO Classification (Table 1). They mostly originate from the germinal centers and encompass atypical *BCL2*-negative germinal centers, an early pattern of large B-cell lymphoma (LBCL) with *IRF4* rearrangement, and “in situ” high-grade B lymphomas. Nybakken et al. published a case series of atypical germinal centers in reactive/non-neoplastic lymph nodes characterized by isolated follicles with germinal centers substantially composed of aggregates of large centroblasts showing atypical mitoses without centrocytes [10]. These atypical follicles do not express *BCL2* by immunohistochemistry and show the absence of *BCL2/IGH* translocation by FISH [10]: the differential diagnoses include a focal involvement by diffuse large B-cell lymphoma (DLBCL) or grade 3B, *BCL2*-negative FL, or a reactive follicular hyperplasia with unusual morphologic features.

Table 1. Lymphoproliferative neoplasms of uncertain biological significance.

	GC Involvement	Non-GC Involvement	Histologic Characteristics	Suggested Procedures When Lymphoproliferative Neoplasms of Uncertain Biological Significance Are Encountered
Entities accepted in the 4th WHO edition				
“In situ” follicular neoplasia (ISFN)	Yes	No	Lack of polarization, closely packed centrocytes with few centroblast.	Exclude pFL and a composite form with appropriate immunohistochemistry. Suggest a complete staging workup to rule out an overt lymphoma in another site.
“In situ” mantle cell neoplasia (ISMCN)	No	Yes	Cyclin D1-expressing B-cells in non-expanded mantle zones of otherwise morphologically reactive lymph node.	Exclude a MCLGP and composite form with appropriate immunohistochemistry. Suggest a complete staging workup to rule out an overt lymphoma in another site.
Entities not included in the in the 4th WHO edition				
Atypical GC BCL2-negative	Yes	No	Isolated follicles with GC composed of aggregates of large centroblast with atypical mitosis without centrocytes and <i>BCL2</i> negative by immunohistochemistry and FISH analysis.	Apply immunohistochemistry to confirm the presence of follicular dendritic networks and the GC origin of the B cell population. Occurrence of strong and diffuse immunoreactivity for IRF4, <i>BCL2</i> , and <i>c-MYC</i> must be assessed. In addition, FISH analysis for <i>IRF4</i> , <i>BCL2</i> , <i>c-MYC</i> rearrangements is advisable. Exclusion of an overt disease with a complete staging workup is mandatory.
Early pattern of large B-cell lymphoma (LBCL) with <i>IRF4</i> rearrangement	Yes	No	Atypical GC enriched with centroblasts, without tingible body macrophages or polarization with strong IRF4 positivity and <i>IRF4</i> rearrangement.	
Single extranodal involvement of “double hit” Follicular lymphoma (DH-FL)	Yes	No	Atypical GC B-cell population with follicular dendritic networks and <i>BCL-2</i> + <i>c-MYC</i> rearrangements.	
Early Burkitt lymphoma (BL)	No	Yes	Aggregates composed of medium-sized lymphoid cells morphologically and phenotypically consistent with BL cells along with mitotic figures and apoptotic bodies	Apply immunohistochemical analysis to characterize the medium size population with BL features added to FISH to identify <i>c-MYC</i> rearrangement
Early classic Hodgkin lymphoma (cHL)	No	Yes	Presence of RS and HL cells in perifollicular areas with preserved lymph node architecture.	Evaluation of the preserved lymph node architecture. Investigate the scattered atypical RS- and HL-cells by immunohistochemistry. Exclusion of an overt disease with a complete staging workup is mandatory.

Early LBL with *IRF4* rearrangement has been reported in one case with predominant follicular hyperplasia that exhibited single atypical germinal centers enriched with centroblasts without accompanying tingible body macrophages displaying expression of CD20, CD10, BCL6, *IRF4/MUM1*, lambda immunoglobulin light chain restriction, and a gain and rearrangement of the *IRF4* gene detected by FISH [11].

Two cases of so-called “in situ” high-grade B lymphomas with *c-MYC* rearrangement have been previously reported [12] as well. By definition, a very low tumor burden was noticed in contrast to other overt B-cell lymphomas with *MYC* gene rearrangements; this feature may suggest that these early “double hit” lesions may require additional genetic hits to progress [12,13]. From a practical perspective, these lymphoproliferations have to be assessed in the context of all clinical findings and accompanied by a strict-follow-up to rule out any possible evolution.

Some operative considerations arise from the previously reported situations. In routine practice, whenever we face potential atypical germinal centers, the immunohistochemical confirmation of the presence of follicular dendritic networks, the germinal center origin of the B cell population, and the occurrence of strong and diffuse immunoreactivity for *IRF4*, *BCL2*, and *c-MYC* must be assessed. In addition, FISH analysis for *IRF4*, *BCL2*, and *c-MYC* rearrangements is advisable. This approach will enable in most instances to rule out, focal area(s) of diffuse large B-cell lymphoma/high-grade B-cell lymphoma “double hit”, partial involvement by grade 3B *BCL2*-negative FL, and early LBCL with *IRF4* rearrangement, respectively. Following the examples of ISFN and ISMCN, the exclusion of an overt disease with a complete staging workup is mandatory in all these cases.

Another niche where early lesions have been described beside the germinal center is monocytoid B-cell hyperplasia [14,15]. Monocytoid B cells (MBCs) were described for the first time by Karl Lennert as immature sinus histiocytosis, representing cells closely related to marginal zone hyperplasia [16]. Morphologically, MBCs measure one-and-a-half to three times the size of small lymphocytes, display round, oval, or indented nuclei with a slightly clumped to vesicular chromatin structure, small and inconspicuous (when present) nucleoli, and abundant pale cytoplasm. These cells can be arranged in perifollicular clusters within and around sinuses and are commonly admixed with scattered neutrophils. Unlike marginal zone B-lymphocytes, MBCs are negative for *BCL2* [17]. Reactive MBCs are frequently associated with follicular hyperplasia and epithelioid macrophages [18] and have been recognized occurring in association with lymphoproliferative diseases, like classic Hodgkin lymphomas (cHL) [19,20]. More recently, clusters of Burkitt cells have been reported with MBC hyperplasia in both immunocompromised and immunocompetent patients [14,15]. In immunocompromised patients, it has been proven that these early lesions carry the risk of progression into an overt Burkitt lymphoma with a worse outcome [14,15].

Different non-Hodgkin lymphomas have been associated with chronic inflammation, either infectious or not. In cases of chronic infection due to non-lymphotropic agents, the pathogen’s role in establishing the proliferation and progression towards overt lymphoma radically differs from other lymphotropic agents. Moreover, IgG4-related disease (IgG4-RD) represents an important topic, as confirmed by the occurrence of a ISFN associated with this condition and presented during the Workshop. IgG4-RD is a fibroinflammatory disorder of uncertain etiology which affects almost any organ [21]. Although most patients with IgG4-RD do not present an association with lymphomas, some cases have been reported to develop concomitant or metachronous low- and high-grade lymphomas [22–28], suggesting that a potential pathogenetic link may lie in the context of a shared chronic antigenic stimulation [22,29,30]. This hypothesis is confirmed by cases #7 and #8 of the Workshop. On these grounds, a practical consideration is that monoclonal rearrangements can be demonstrated in a nonmalignant, antigen-driven proliferation of B cells, such as autoimmune disorders; accordingly, additional criteria of malignancy must be fulfilled to efficiently differentiate neoplastic proliferations from reactive conditions in this setting [31].

2. Submitted Cases of ISFN and ISMCN Associated with Overt Lymphoma

2.1. Case n. 1

Dr. Magnoli presented the previously published case [32] of a 75-year-old woman with multiple and bilateral lymphadenopathies that underwent an excisional biopsy of a right cervical lymph node. Morphological and immunohistochemical findings allowed to conclude for a diagnosis of a composite lymphoma encompassing FL, grade 1 to 2, “in situ” mantle cell neoplasia (ISMCN), and MCL with mantle zone growth pattern (MCLGP). A stage IVA was assessed, and the patient was treated with eight cycles of R-CVP (Rituximab plus a combination of Cyclophosphamide, Vincristine, and Prednisone) regimen, obtaining a complete remission. After two years, diffuse lymphadenopathy appeared, and the subsequent biopsy revealed a low-grade FL without any signs of a neoplastic mantle cell component, and after four years of “watch and wait”, a progression of the disease was documented; the patient died of lymphoma after being treated with a new line of chemotherapy with eight cycles of Chlorambucil chemotherapy, followed by a steroid-based support therapy. Karyotype and Spectral Karyotyping (SKY) FISH analyses on metaphases performed on the first biopsy tissue sample confirmed different cell clones. The neoplastic clone carrying the t(11;14) translocation involving *CCND1* did not show additional cytogenetic abnormalities, whereas the neoplastic cell population with the t(14;18) translocation involving *BCL2* was characterized by a triploid karyotype with several additional alterations, including also the rearrangement of *BCL6*. In this context, the observations led the authors to suggest that the progressively aggressive behavior of this B-cell lymphoma was determined by the complex karyotype of the overt FL [32]. On the contrary, the ISMCN did not harbor additional genetic abnormalities, nevertheless not affecting the clinical outcome [32]. Therefore, the following case confirms that the occurrence of additional genetic aberrations may drive progression and clinical outcomes.

2.2. Case n. 2

Dr. Granai discussed the case of a 45-year-old male who underwent the excisional biopsy of an enlarged axillary lymph node following the diagnosis of MCL of the appendix. The lymph node architecture was replaced by a diffuse proliferation of small monotonous lymphocytes with round nuclei and scant cytoplasm surrounding hyperplastic follicles with regularly structured germinal centers (Figure 1). Immunohistochemical investigations demonstrated the presence of two distinct lymphoid populations. The interfollicular cells were immunoreactive for CD20, CD5, CD23, and LEF1 (Figure 2). Cyclin D1 and SOX11 were expressed by reduced mantle zones surrounding reactive lymphoid follicles and absent in the interfollicular areas. Accordingly, a composite ISMCN and small lymphocytic lymphoma (SLL) diagnosis was made. IgH rearrangement confirmed the existence of two clonally unrelated B-cell neoplastic populations. The present case describes the well-known combination of ISMCN and SLL [33], exemplifies the concept that “in situ” lymphoma might be observed in association with overt MCL in distant sites, and highlights that the significance of the early lesion remains uncertain, thus suggesting that the clinical evaluation for evidence of overt lymphoma is highly recommended.

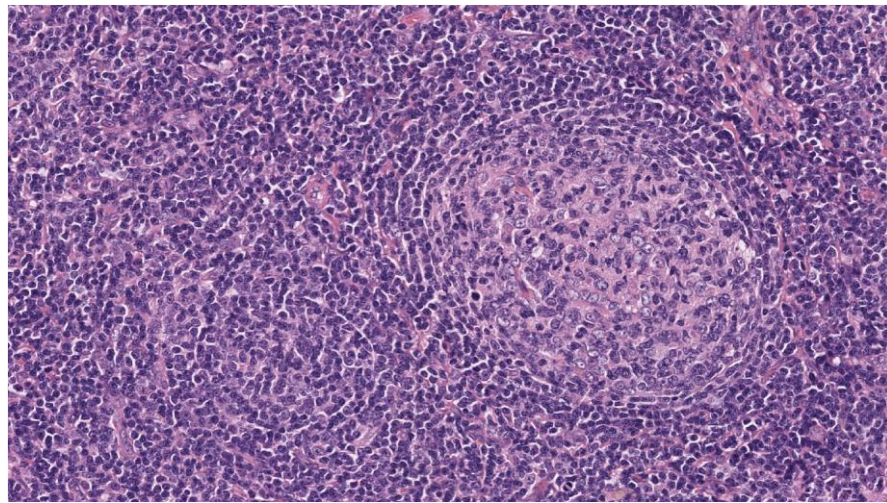


Figure 1. H&E original magnification 20×. The lymph node architecture is replaced by a diffuse, interfollicular monotonous proliferation of small lymphocytes with round nuclei and scant cytoplasm surrounding hyperplastic follicles with regularly structured germinal centers.

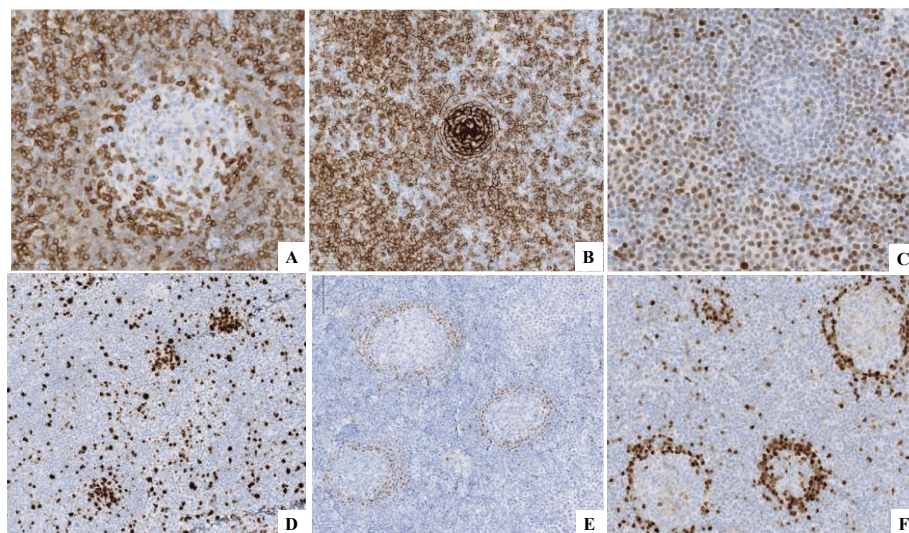


Figure 2. (A) CD5+ in both components. (B) CD23+ in the SLL component. (C) LEF1+ in the SLL component. (D) Ki-67 highlights the proliferation centers. (E) Cyclin D1+ in the ISMCN. (F) SOX11+ in the ISMCN.

2.3. Case n. 3

Dr. Di Stefano submitted the case of a 45-year-old male patient that received a diagnosis of chronic lymphocytic leukemia (CLL) with atypical phenotype according to a bone marrow biopsy and the flow cytometric analysis results. The bone marrow biopsy showed a diffuse interstitial infiltrate of small B lymphocytes with a round nucleus and scant cytoplasm, immunoreactive for CD20, BCL2, and CD5 and negative for CD23, Cyclin D1, SOX11, CD10, and BCL6. A few weeks later, the patient underwent an excisional biopsy of three small cervical lymph nodes. The lymph node architecture was effaced by a small-to-medium-sized population with an immunophenotypic profile consistent with CLL with an atypical phenotype [34,35]. Two residual follicular structures were present, and their germinal centers showed a strong immunoreactivity for CD10 and BCL2 with a low proliferation index. The final diagnosis was CLL with an atypical phenotype and ISFN. In the present case, it is also confirmed that ISFN can be associated with other forms

of overt lymphoma such as CLL. In such an event, it is necessary to always report the early lesion to guarantee appropriate clinical management.

3. Submitted Cases of Early Lymphoproliferative Lesions Originating from the Germinal Center Other Than ISFN and ISMCN

3.1. Case n. 4

Dr. Lazzi submitted the case of a 77-year-old male patient that underwent radical prostatectomy with bilateral lymphadenectomy for prostatic adenocarcinoma. Within one of the right iliac-obturator lymph nodes, two isolated follicles (Figure 3A–C) displayed germinal centers with atypical features such as the absence of polarization and enrichment of centroblasts. The atypical follicles were positive for B-cell and germinal center-related markers but negative for BCL2 by immunohistochemistry and for *BCL2* translocation by FISH analysis (Figure 3D–F). An overt FL grade 3A was found in a contralateral lymph node (Figure 3G,H), which was negative for BCL2, as well both by immunohistochemistry and FISH; therefore, the final diagnosis was of FL, grade 3A with focal localization on the contralateral lymph node. The histologic interpretation of isolated atypical germinal centers can be challenging, but an overt FL helped achieve the correct diagnosis. A Next-Generation Sequencing (NGS) analysis was performed using an Illumina custom 80-gene-targeted NGS panel for B-cell lymphomas and revealed genetic variants in *TNFAIP3* and *NOTCH2*.

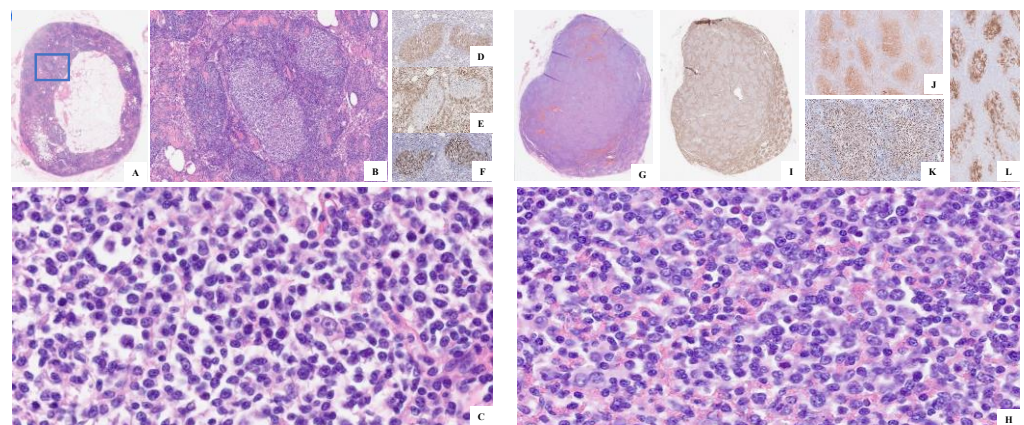


Figure 3. (A) H&E original magnification 2× of the right iliac-obturator lymph node displaying two atypical follicles highlighted in the blue rectangle. (B) H&E original magnification 10× of the atypical follicles. (C) H&E original magnification 40× of the atypical germinal centers with the absence of polarization and enrichment in centroblasts. (D) CD10+, (E) BCL2-, and (F) Ki67 immunostains. (G) H&E original magnification 4× of the left iliac-obturator lymph node. (H) H&E original magnification 40x of the overt FL on the left iliac-obturator lymph node. (I) BCL2-. (J) CD10+. (K) Ki67. (L) CD23 immunostains.

3.2. Case n. 5

Dr. Granai submitted and recently published [36] the case of a 72-year-old woman without significant medical history that underwent colonoscopy for enduring complaints and constipation; a 5-mm sessile polypoid lesion in the sigmoid colon was noted. Microscopically, the polypoid lesion displayed a submucosal lymphoid infiltrate with a follicular growth pattern and predominant centroblasts, along with very few centrocytes. The lymphoid population showed immunoreactivity for CD20, CD10, BCL6, BCL2, and MYC, in the context of expanded and disrupted follicular dendritic meshworks. FISH studies identified both *IGH/BCL2* and *IGH/MYC* gene rearrangements, allowing the diagnosis of an extranodal FL grade 3A, with *BCL2* and *MYC* rearrangements (DH-FL). Staging did not show additional sites of disease, and the patient is currently in good health and has never progressed. This case raises several questions related to patient's management, since it is not clear whether to consider DH-FL an indolent lymphoma based on its morphologic

aspects or an aggressive lymphoma given its cytogenetic features [37–41]. This dilemma related to the outcome is further enhanced when DH-FL displays partial involvement or is limited to a single site. More studies are needed to clarify this issue.

4. Submitted Cases of Early Lymphoproliferative Lesions Arising in the Setting of Monocytoid Hyperplasia

Case n. 6

Dr. Di Stefano presented the case of a 61-year-old woman with a prior history of invasive breast carcinoma treated with surgical resection, chemotherapy, and radiotherapy, who during follow up developed left supraclavicular lymphadenopathy. The excised lymph node showed follicular hyperplasia with polarized germinal centers; in the perifollicular areas, aggregates of MBC were admixed with rare, scattered large mononucleated or binucleated cells equipped with eosinophilic nucleolus and basophilic cytoplasm (Figure 4). The large cells were immunoreactive for CD30, CD15, PAX5 weak (Figure 5), and MUM1 and negative for CD20, CD3, and CD45. EBV was negative by EBER in situ hybridization. The molecular analysis performed on microdissected atypical, perifollicular areas detected a polyclonal IGH rearrangement, supporting the diagnosis of partial involvement by cHL. Since the radiologic and clinical evidence showed a localized disease, a “watch and wait” approach was chosen, and in the following years, subsequent nodal biopsies of the supraclavicular lymph nodes displayed the same morphological picture. Five years after the first diagnosis, the patient exhibited left inguinal lymphadenopathy and underwent an incisional biopsy. The morphologic examination revealed a subverted architecture by small T lymphocytes, eosinophils, and histiocytes intermingled with classical Reed–Sternberg (RS) and Hodgkin cells (Figure 6). The morpho–phenotypical profile was consistent with cHL, mixed cellularity. After the diagnosis, the patient received appropriate chemotherapy but had frequent hospitalizations due to recurrent nosocomial infections. The following case demonstrated an overt cHL after a history of partial involvement of cHL developing within the context of MBC hyperplasia.

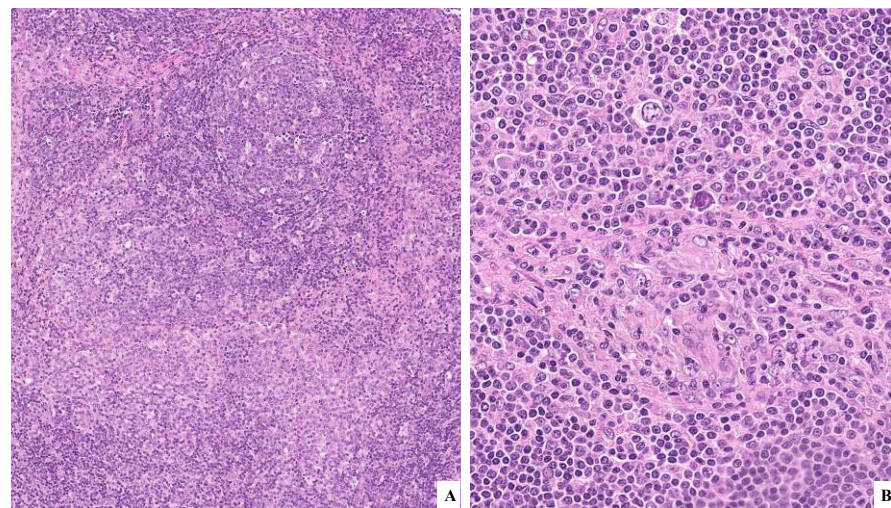


Figure 4. (A) H&E original magnification 10× displaying follicular hyperplasia with polarized germinal centers and, in the perifollicular areas, aggregates of MBC. (B) H&E original magnification 20× showing, in the perifollicular areas, MBC mixed with rare large mononucleated or binucleated cells containing an eosinophilic nucleolus and basophilic cytoplasm.

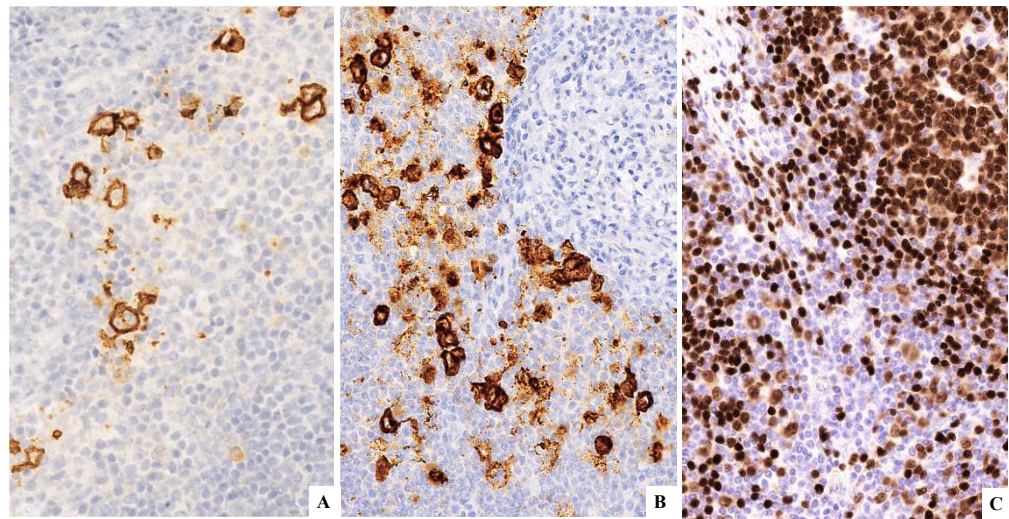


Figure 5. (A) CD30+. (B) CD15+. (C) PAX5+ weak.

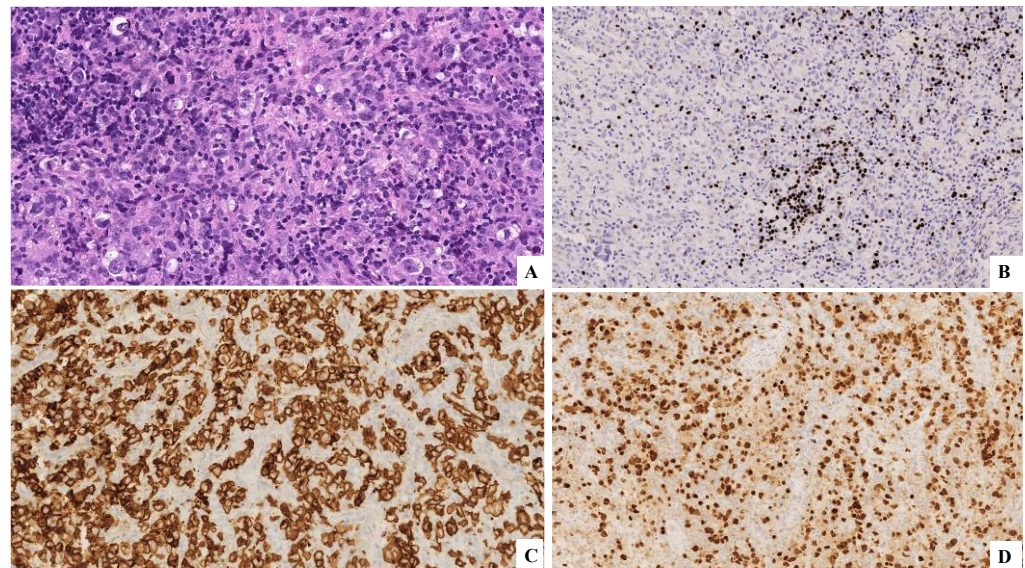


Figure 6. (A) H&E original magnification 20× that displays small T lymphocytes, eosinophils, histiocytes, classical Reed–Sternberg cells, and Hodgkin cells. (B) PAX5-. (C) CD30+. (D) MUM1+.

5. Submitted Cases of Early Lymphoproliferative Lesions Associated with Infectious Diseases and Chronic Inflammation

5.1. Case n. 7

Dr. Vittone presented the case of a 76-year-old man with weight loss and low-grade persisting fever for many months. The PET-CT scan revealed multiple lymphadenomegaly on both sides of the diaphragm with high spleen, bone, and left colon uptake. Histological examination of an axillary lymph node showed an area with well-formed granulomas composed of epithelioid histiocytes and occasional Langhans-type giant cells with central eosinophilic necrosis (Figure 7A). A PCR analysis performed on the paraffin-embedded tissue confirmed the presence of *Mycobacterium tuberculosis* DNA. The residual portion of the lymph node showed predominant follicular hyperplasia; herein, immunohistochemical investigations highlighted two follicles with strong staining for CD10, BCL2 (Figure 7C,D) with a low proliferation index suggestive of ISFN. Therefore, a diagnosis of necrotizing granulomatous lymphadenitis due to *Mycobacterium tuberculosis* infection associated with ISFN was made.

5.2. Case n. 8

Dr. Santi presented a case of a 77-year-old male with a prior history of prostatic adenocarcinoma. During follow-up, left hydronephrosis due to a retroperitoneal mass of 6.5 cm in the maximum diameter developed. The histological examination of left subtotal ureterectomy displayed follicular hyperplasia and predominant mature IgG4+ interfollicular plasma cells with a high IgG4/IgG ratio within the background of septal, storiform fibrosis (Figures 8 and 9). Within this background, a single atypical follicle unusually constituted by monomorphous centrocytes, few centroblasts, and attenuated mantle zones was noticed with a strong positivity for BCL2 and CD10 (Figure 10). A PCR analysis showed a monoclonal IgH rearrangement. The final diagnosis was IgG4-RD with ISFN. A few months after the diagnosis, the patient died of complications due to sepsis.

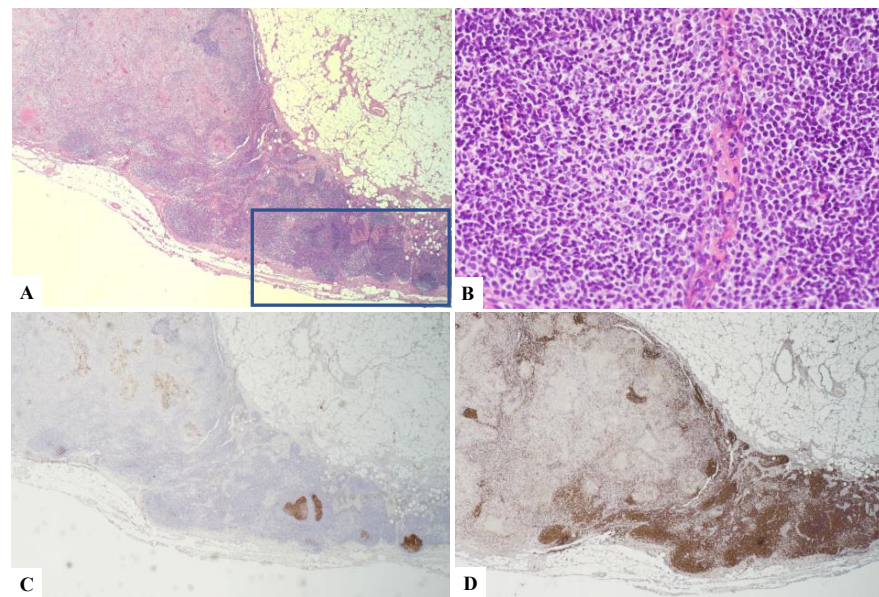


Figure 7. (A) H&E original magnification 2.5× of the axillary lymph node displaying an area with well-formed granulomas, and in the remaining part of the lymphoid tissue, follicular hyperplasia was observed with two atypical follicles (blue rectangle). (B) H&E original magnification 40× of one of the atypical follicles suggestive of ISFN. (C) CD10+. (D) BCL2+.

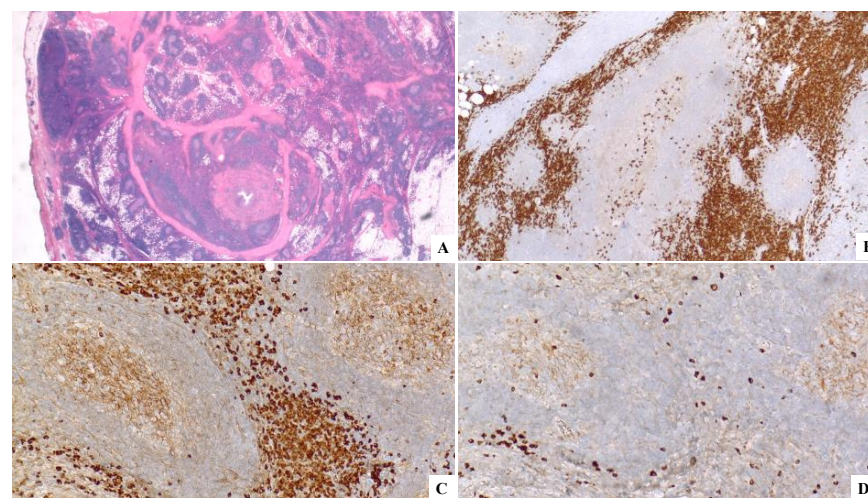


Figure 8. (A) H&E original magnification 2× displaying a lymphoproliferative lesion in the background of septal, a storiform fibrosis. (B) CD138+. (C, D) A Kappa light chain restriction.

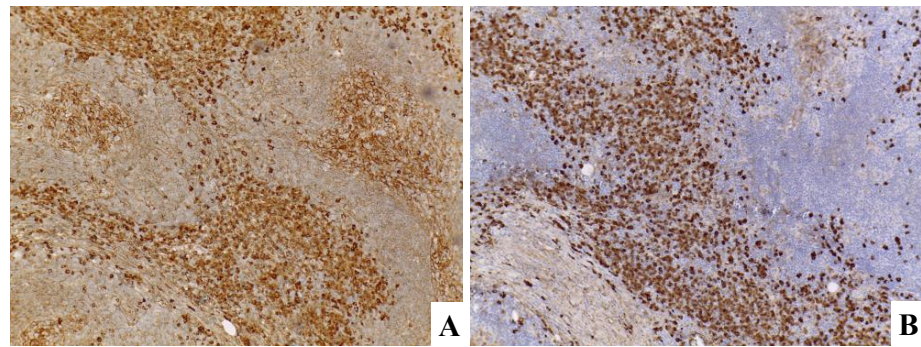


Figure 9. (A) IgG. (B) IgG4.

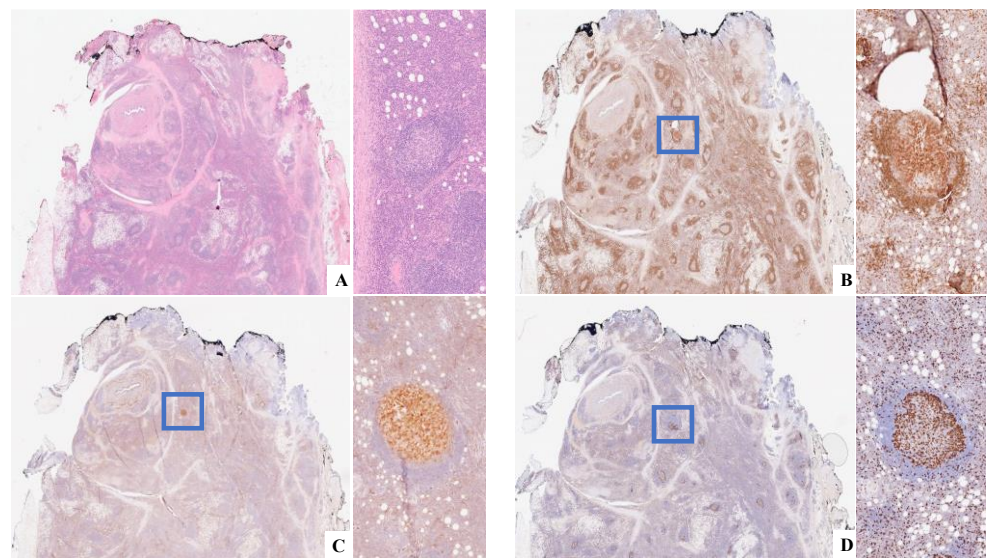


Figure 10. (A) H&E original magnification 4× ISFN highlighted in the blue rectangle. (B) BCL2+. (C) CD10+; (D) Ki-67.

6. Conclusions

Early/in situ lymphoproliferative disorders are still an unclear subject since the evolution of these diseases at the time of the diagnosis is unpredictable on morpho-phenotypical-molecular-cytogenetic grounds. The sequence precancer–cancer in epithelial malignancies does not necessary overlap with the relationship between early lymphoproliferative lesions and overt lymphoma. In fact, most early lymphoid lesions do not progress to an overt lymphoma and may be concomitant with these latter. In the cases presented during the Workshop, the entities ISFN and ISMCN, already recognized by the 4th edition of the WHO classification, were associated with other overt lymphoproliferative processes, and therefore considered a composite lymphoma (Table 2).

Table 2. Clinical cases presented during the Workshop.

Case	Gender	Age	Diagnosis	Presence of Overt Lymphoma	Type of Overt Lymphoma
Case n. 1	F	75 y	FL and ISMCN	Yes	FL
Case n. 2	M	45 y	ISMCN and SLL	Yes	MCL in previous biopsy
Case n. 3	M	45 y	CLL with atypical phenotype and ISFN	Yes	CLL on bone marrow
Case n. 4	M	77 y	FL, 3A with focal localization on the contralateral lymph node	Yes	FL, 3A
Case n. 5	F	72 y	Extranodal FL with <i>BCL2</i> and <i>c-MYC</i> rearrangement	No	
Case n. 6	F	61 y	Early cHL in monocytoid hyperplasia	Yes	cHL, mixed cellularity
Case n. 7	M	76 y	Necrotizing granulomatous lymphadenitis associated with ISFN	No	
Case n. 8	M	77 y	IgG4-RD with ISFN	No	

The current view of the progression in lymphoproliferative lesion postulates that this process relies on a multistep sequence rather than only on a single event. This concept is exemplified by case #1, confirming that the development of a complex karyotype is the primary cause of the disease's evolution [32], while case #2 highlights the importance of recognizing these early lesions to inform the clinician and carefully look for a possible overt and different lymphoma in another site. In case #3, the association of CLL with an atypical phenotype and ISFN was reported demonstrating that these early lesions concurrent with other lymphoproliferative processes may also be incidental findings discovered by immunohistochemistry. Nevertheless, the observation of such cases, which are usually unrelated to malignant overt counterparts, raises the question of whether there could be an underlying susceptibility for developing B lymphoproliferative processes in certain subjects [42]. The germinal centers are a fragile environment where neoplastic processes can develop. Notwithstanding the overexpression of antiapoptotic molecules such as *BCL2* as a result of t(14;18) has been recognized to spy on the occurrence of FL, and case #4 displays that the histopathological examination can be sometimes the only key feature to unravel a lymphoproliferative process. In this case, the lymphoproliferative lesion was suspected on morpho-phenotypic features in two germinal centers, although there was a lack of *BCL2* positivity. In this context, the finding of the overt FL on the contralateral lymph node aided the diagnosis of FL t(14;18)-negative that has been proven to be a genetically heterogeneous entity [43], and the NGS analysis performed on the case documented the presence of frequent mutations that have been detected in FL t(14;18)-negative, namely *TNEAIP3* and *NOTCH2* [43]. Therefore, we point out that occasional atypical follicles *BCL2*-negative in the context of a reactive lymph node should suggest the exclusion of an FL t(14; 18)-negative in other sites. A close correlation between molecular data and morphology is always required, since several studies have detected clonal populations in the context of classical reactive germinal centers or hyperplastic marginal zones [44,45].

In the "early" extra nodal DH-FL (case #5) [36], additional genetic hits are considered necessary for the full transformation of these 'aggressive' in situ neoplasms to a clinically overt disease [12,13]. Furthermore, once these lesions are recognized, clinical characteristics drive treatment decisions, and a close follow-up is mandatory to rule out overt lesions in another site.

Moving outside the germinal center, more specifically in the context of MBC hyperplasia, we notice a possible role of MBC in controlling the neoplastic disease [15,19,20]. In fact, in case #6, all the subsequent biopsies displayed RS cells closely associated with clusters of MBCs, and two previous studies have documented this aspect in overt cHL [19,20]. It has been established that the HL/RS cells originate from the germinal centers [46], and when they migrate to the perifollicular areas, they probably trigger a reaction like MBC hyperplasia. Therefore, even in cHL, MBC hyperplasia may be a physiologic antitumor mechanism of the host that counteracts the development of the full-blown disease [15,19,20].

In the presence of infectious diseases and chronic inflammation syndromes, an underlying lymphoproliferative process, may occur and should be considered. Rarely, non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma were concurrent with chronic infection by *Mycobacterium tuberculosis* and the *Mycobacterium avium* complex [47–55]. Setting aside patients with congenital and cell-mediated immunity defects, it has been hypothesized that *Mycobacterium tuberculosis*, similarly to *Helicobacter pylori*, might induce rearrangements more readily than other infectious agents, since they are both intracellular pathogens [53]. Much caution must be applied in the event of an IgG4-positive lymphoma or plasma cell neoplasm when numerous IgG4+ plasma cells are noticed in the context of a lymphoplasmacytic proliferation [56], and a clinical correlation might be necessary. To our knowledge, a case of necrotizing granulomatous lymphadenitis due to *Mycobacterium tuberculosis* infection and IgG4-RD concomitant to an early lesion have not been reported. Moreover, during the Workshop, it was suggested that the chronic inflammatory process, either created by an infectious agent or by an inflammatory disorder, could be the trigger determining an early lymphoproliferative form. However, to be added to the following hypothesis, we should also consider the well-known role of immunosurveillance of the microenvironment in B-cell lymphomas [15]; therefore, further studies could highlight the control mechanisms and the events determining the onset and progression to an overt disease.

In conclusion, pathologists should emphasize that the above-described early/in situ lesions retain an uncertain potential of malignant progression and require a strong integration with the clinical and imaging findings. Given that, presently, the therapeutic strategy relies on the diagnosis of an overt lymphoma, a conservative management accomplished by an active follow-up must be considered in these early/in situ lymphoproliferations.

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