Case Report

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# Composite Lymphoma Comprising Follicular Lymphoma with In-situ Mantle Cell Neoplasia: A Case Report and Review of the Literature

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## Abstract

A 55-year-old gentleman presented to our hospital with a single inguinal adenopathy, and no other clinical symptoms or signs. An excisional lymph node biopsy was performed. Pathologic evaluation demonstrated follicular center site which stained positive for CD20, CD10, Bcl-2, Bcl-6, and mantle zone cells which demonstrated Cyclin D1 (CCND1) positivity, partial SOX11 positivity and no expression of CD5, suggesting the diagnosis of composite lymphoma comprising follicular lymphoma (FL) with in situ mantle cell neoplasia (ISMCN), the latter previously referred as in situ mantle cell lymphoma (MCLIS). FL is known as indolent non-Hodgkin lymphoma; however, the clinical significance of a coexisting ISMCN continues to be elusive, and optimal management of these patients remains largely unknown. This paper reports a new case of this extremely uncommon condition and also discusses reviews of the literature including advances in molecular pathogenesis and lymphoma genomics with the aim to offer novel insights into this rare hematological malignancy.

***Keywords***: *Haematopathology, Composite lymphoma, Follicular lymphoma, In situ mantle cell neoplasia*

## Introduction

Composite lymphoma (CL) is a fascinating process consisting, by definition, of two or more morphologically and immuno-phenotypically distinct lymphomas within the same anatomic site [1]. Their frequency ranges from 1% to 4.7% of total lymphomas, making them a rare finding, which is mostly incidentally observed [2]. Regardless of their different histology, in some cases these lymphomas can be clonally related [3], whereas in others they are not, representing the "collision" of two clonally unrelated tumors. The majority of reported cases are B-cell lymphomas combined with Hodgkin lymphoma, however the combination of two different B-cell lymphomas, or composite B-cell and T-cell lymphomas have also been reported [2, 4]. CL with FL and mantle cell lymphoma (MCL) are extremely rare, and, to our knowledge, so far only 7 cases of composite FL and in situ mantle cell neoplasia (ISMCN) have been described [4, 5]. These cases were more often incidental and associated with indolent clinical course, since only rare cases had progressed to overt lymphoma, with the ISMCN component generally not evolving in an aggressive disease and the treatment and outcome of patients driven by the progression of the sole FL component [4]. This is typically low-grade, Bcl2 positive and harbors the t(14;18) translocation, whereas the ISMCN component shows an in situ mantle-zone growth pattern, it is CCND1 positive and harbors the t(11;14) translocation [5]. Some studies suggest that FL and MCL are often clonally related [3, 4].

## Case Report

A 55-year-old male presented to the Hematology Unit of our hospital with a painless nodular mass of 3 x 4 cm which was sited just above the right inguinal ligament. This tumefaction had appeared a few months earlier without any other associated symptom, and the patient had reports of normal CBC, coagulation and serology parameters. An excisional biopsy was performed. This showed subversion of the lymph node normal structure by a nodular infiltrate characterized by extracapsular extension with sclerosis (Fig. 1 A) and the proliferation of small cleaved lymphoid cells (centrocyte-like) mixed to large non-cleaved cells (centroblast-like) (Fig. 1B), which were always less than 6 when counted for high power field (HPF). At immunohistochemical analysis, these cells were positive for

CD20, CD10, Bcl2 (Fig. 2A) and Bcl6 (Fig. 2B), and showed focal expression of MUM1 while were negative for TdT. Ki67 proliferation index was 50%. A conserved meshwork of CD21+CD23+ disarranged follicular dendritic cells was also present as well as small inter- and intra-follicular CD3+CD5+ T lymphocytes and rare CD30+ immunoblasts. Unexpectedly, immunostaining for Cyclin D1 highlighted the presence of small mantle cell-like lymphocytes lodged in the mantle cuffs of a number of neoplastic follicles (Fig. 2C), and some of these cells co-expressed SOX11 (Fig. 2D). Based on these morphological and immunohistochemical findings, a diagnosis of grade 2 B-cell follicular non-Hodgkin lymphoma, with coexisting, in situ mantle cell neoplasia (ISMCN) was made, according to the 2017 WHO criteria [6].

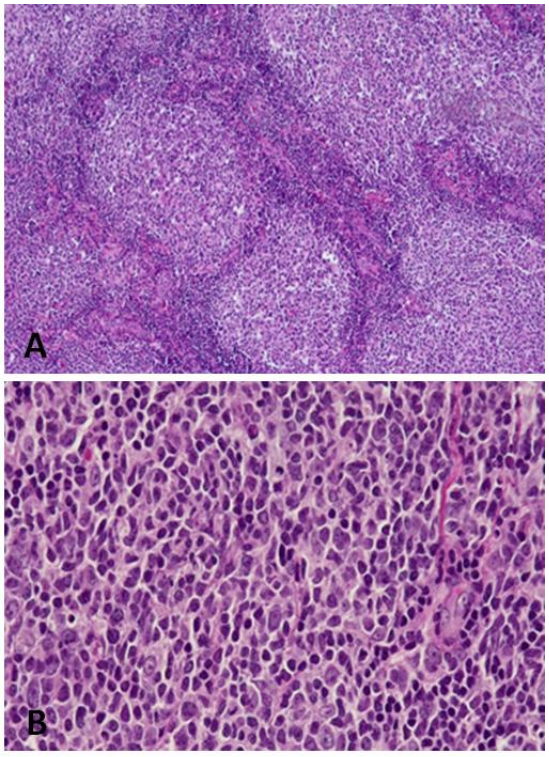


***Figure 1: Histopathological features A) Subversion of the lymph node normal structure by a nodular infiltrate (H&E X100). B) Details of a neoplastic follicule with proliferation of small cleaved lymphoid cells (centrocyte-like) mixed to large non-cleaved cells (centroblast-like) (H&E X200).***

## Discussion

CL composed by follicular (FL) and mantle cell lymphoma (MCL) are particularly rare and yet not fully characterized. It has been reported that the neoplastic clones of MCL carry the t(11;14) translocation involving cyclin D1, a hallmark of MCL, while generally lack additional cytogenetic alterations

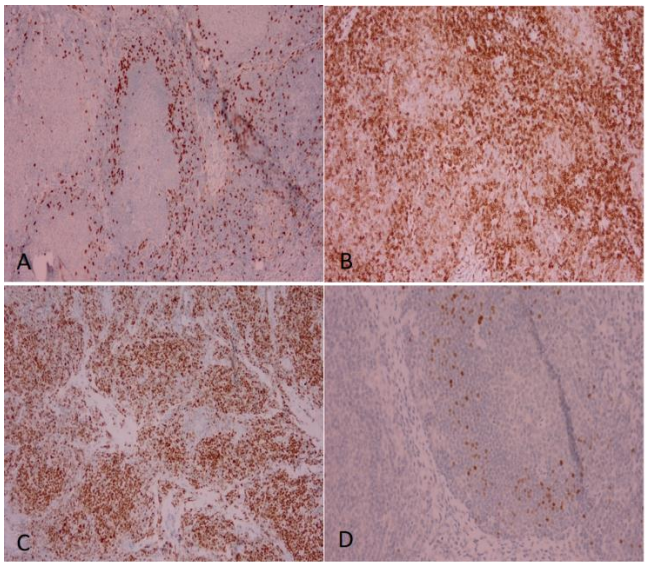


***Figure 2: Immunohistochemical features A) Centrocyte-like and centroblast-like lymphoid cells showed Bcl-2 positive stain, x100. B) Centrocyte-like and centroblast-like lymphoid cells showed Bcl-2 positive stain, x100. C) Small mantle cell-like lymphocytes lodged in the mantle cuffs of neoplastic follicles showed Cyclin D1 positive stain, x 200. D) Some small mantle cell-like lymphocytes showed SOX11 positive stain, x 200.***

and do not evolve in an overt MCL. However, appearance of secondary genetic alterations, such as deletions and mutations of TP53 (at 17p), CDKN2A-CDKN2B (at 9p), RB1 (at 13q4), and ATM (at 11q), as well as amplifications of MYC (at 8q24), BM1 (at 10p13), and CDK4-MDM2, are able to induce the development of an overt MCL [7]. Two clinically and biologically distinct types of lesions characterized by cyclin D1-positive cells limited to the mantle zones of reactive follicles have been described: “in situ mantle cell lymphoma” (MCLIS), recently referred to as “in situ mantle cell neoplasia” (ISMCN) [6], which presents with relatively few cyclin D1-positive cells restricted to the mantle zone, and “mantle cell lymphoma with a mantle zone growth pattern”, a lesion characterized by the presence of more extensive cyclin D1-positive cells within the mantle zone plus focal extension into the inter-follicular areas. While the first may represent the very initial steps of MCL lymphomagenesis, the latter would correspond to the early or partial lymph node involvement of a conventional MCL, similarly to what has been already described for follicular lymphomas [8]. In line with this, it is the recent detection of clonal B cells restricted to the germinal centers carrying the t(14;18) translocation [9, 10], a phenomenon which could be interpreted as an early step in the lymphomagenesis of follicular lymphoma, possibly corresponding to ISMCN,

and referred to as follicular lymphoma in situ (FLIS) [9]. As the existence of very tiny clones carrying the t(11;14) translocation with no evidence of progression to overt lymphoma has been found in the peripheral blood of 7% of healthy individuals [11], ISMCNs could reasonably correspond to their tissue counterpart. Interestingly, most of these cases also presented clones with the t(14;18), and therefore the concomitant identification of clones with both translocations in the same healthy individual might suggest that in certain cases a same person may have a specific susceptibility to develop and expand aberrant B-cell clones. However, the follow-up of these individuals has indicated that in most cases ISMCNs do not progress to an overt MCL for even long periods of time (1 to 19.5 years), also in the absence of any kind of treatment [4]. Such a quite slow and relatively infrequent evolution of ISMCNs would be consistent with another study in which it was found that seven patients already presented an ISMCN lesion 2-15 years (median 8 years) before the onset of an overt MCL lymphoma [12]. A t(11; 14) (q13; q32) translocation resulting in the juxtaposing of the proto-oncogene CCND1 to the immunoglobulin heavy chain (IGH) complex is considered the pivotal event in the development of MCL. This translocation occurs within the bone marrow during pre-B stage differentiation with V(D)J recombination of the IGH variable region (IGHV) [13], suggesting that naive B cells carrying t(11; 14) would colonize the mantle zone of the lymphoid follicle and then give rise to an ISMCN. Despite ISMCN and FL are often clonally unrelated and mutually exclusive, previous studies have shown that in at least 15–40% of these CLs, the two components carry IGHV hyper-mutations with identical dominant monoclonal peaks [3], implying that both lymphomas might initially originate from a same pre-neoplastic clone and subsequently diverge. Interestingly, another prove of this hypothesis derives from a study of CL consisting of two clonally related FL and ISMCN lesions, in which the Epstein-Barr virus (EBV) DNA was detected only in the FL but not in the ISMCN cells, indicating that these two neoplastic clones had split into two early during the development of the CL [14]. SOX11 is a specific marker expressed in 78–93% of MCLs [15]. A recent study showed that SOX11 expression is much less common in ISMCN than in MCL with mantle zone pattern and/or overt MCL [7], with only 44% of ISMCNs expressing SOX11, suggesting that when ISMCNs express SOX11 they might have a greater tendency to progress, however, both SOX11-negative and -positive lesions have an indolent behavior. SOX11-positive cells of ISMCNs are genetically unstable, whereas their counterpart is genetically stable, possibly representing the very early precursors of neoplastic naïve B-cells harboring t(11; 14) which just entered the lymph node germinal centers [7]. ISMCN can be divided into two further groups: CD5-negative and CD5-positive, with the first typically seen in younger patients, often presenting with nodal involvement and no need of treatment, and the latter generally associated with older age, extra-nodal involvement, and higher probability to require treatment. Despite of that, no difference in survival has been noted between these two groups [15]. No guidelines have been established for the staging and management of ISMCNs, as most of these patients are not expected to develop an overt MCL, only requiring to be followed up for long periods of time without any treatment [7]. ISMCN must be distinguished from both mantle cell lymphoma with a mantle zone pattern and overt mantle cell lymphoma because the latter conditions generally require treatment, and staging is required. Currently, it is unknown whether ISMCNs are always true pre-neoplastic lesions which ultimately will progress to overt lymphomas or they are characterized by a low chance of progression, so CLs consisting of concomitant FL and ISMCN can pose diagnostic and therapeutic challenges. However, with new advances in molecular pathology and lymphoma genomics, we have now more opportunities to investigate these conditions and to gain novel insights necessary to improve patients' treatment.

## Conclusion

While in some cases the FL and ISMCN components of CL are clonally related, in others they represent the "collision" of two clonally unrelated tumors [4]. Their finding is incidental, with the ISMCN component generally not evolving in an aggressive disease, and the treatment driven by the progression of the sole FL component [4]. This is typically low-grade, bcl2 positive and harbors the t(14;18) translocation, whereas the ISMCN component shows an in situ mantle-zone growth pattern, it is Cyclin D1 positive and harbors the t (11;14) translocation.

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