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Synchronous immunophenotypically and clonally distinct follicular lymphoma and marginal zone lymphoma with massive amyloid deposition

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ABSTRACT

Follicular lymphoma (FL) and marginal zone lymphoma (MZL) are distinct clinicopathologic entities derived from small B-cells. Here we report an unusual case of simultaneous occurrence of CD10-negative, *t(14;18)/BCL2*-negative FL with rare residual germinal centers, and extranodal MZL with extensive amyloid deposition. Diagnostic challenges included a prominent nodular growth pattern and lack of expression of commonly used germinal center (GC) B-cell markers and the *t(14;18)/BCL2* gene rearrangement characteristic of FL in an inguinal lymph node. The corresponding chest wall mass was diagnosed as MZL with extensive amyloid deposition. Though initially diagnosed as MZL involving a lymph node corresponding to the chest wall mass, newer markers of GC B-cells, HGAL and LMO2, as well as a newly described marker of marginal zone cells, MNDA, were helpful to establish the diagnosis of FL in the inguinal lymph node. Subsequent molecular clonality studies showed two distinct clonal B-cell processes in the two sites. This case illustrates the need for integration of morphologic findings with careful choice of ancillary diagnostic tests to establish definitive diagnoses among the spectrum of lymphomas derived from small B-cells.

1. Introduction

Lymphomas derived from small B-cells exhibit a spectrum of clinical behavior and include indolent lymphomas that may not require treatment to those that have a propensity to transform to an aggressive lymphoma or remain refractory to therapy [1]. These lymphomas include follicular lymphoma (FL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), and hairy cell leukemia (HCL) [1]. Clinically, patients may be asymptomatic or present with lymphadenopathy, splenomegaly, systemic symptoms or cytopenia arising from bone marrow involvement. Although accurate diagnosis of this spectrum of lymphomas is important for appropriate clinical management, specific markers for definitive subclassification are not always available.

The separation of FL from nodal MZL can be particularly challenging in a subset of cases where there is a nodular growth pattern: FL infiltrates may extend into the interfollicular space and show diffuse involvement or marginal zone differentiation [2,3], mimicking MZL, whereas MZL may show follicular colonization [4,5]. A subset of FL may also lack expression of commonly used GC B-cell markers such as CD10 and BCL6. Although HGAL and LMO2 are newer sensitive and specific markers for FL [6–8], they are not always employed in routine immunohistologic panels. Fluorescence in situ hybridization (FISH) for the *t(14;18)/BCL2* gene rearrangement is very helpful in the diagnosis of FL, although a subset of FL lack this translocation. MZL has a less distinct immunophenotype, but co-expression of CD43 on B-cells, expression of MNDA [9,10], or the *AP12-MALT1* translocation, when present, may aid in the diagnosis of MZL.

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Table 1
Reagents and conditions used for immunohistochemistry

Antibody	Clone	Dilution	Platform/Conditions	Manufacturer
CD20	L26	1:1000	Ventana XT; Standard retrieval	Dako, Capinteria, CA
CD79a	JCB117	1:40	Ventana XT; Standard retrieval	Dako, Capinteria, CA
CD3	Rabbit polyclonal	1:50	Ventana XT; Standard retrieval	Cell Marque, Rocklin, CA
CD5	4C7	1:100	Ventana XT; Standard retrieval	Leica, Newcastle-upon-Tyne, UK
BCL2	E17	1:50	Leica Bond-Max; ER2 retrieval	Epitomics
CD10	56C6	1:80	Leica Bond-Max; ER2 retrieval	Leica, Newcastle-upon-Tyne, UK
BCL6	GL191E/A8	1:100	Ventana XT; Standard retrieval	Cell Marque, Rocklin, CA
HGAL	MRQ	1:100	Leica Bond-Max; ER2 retrieval	Cell Marque, Rocklin, CA
LMO2	1A9-1	1:4	Leica Bond-Max; ER2 retrieval	Ventana, Tucson, AZ
MNDA	235A/G1	1:50	Leica Bond-Max; ER2 retrieval	Courtesy of G. Roncador, CNIO, Spain
BCL1	SP4	1:50	Ventana XT; Standard retrieval	Thermo-Fisher Scientific
IgA	NICLA	1:200	Ventana XT; Standard retrieval	Leica, Newcastle-upon-Tyne, UK
IgG	RWP49	1:400	Leica Bond-Max; ER2 retrieval	Leica, Newcastle-upon-Tyne, UK
IgM	Polyclonal	1:1250	Ventana XT; Standard retrieval	Dako, Capinteria, CA
Kappa	Rabbit polyclonal	1:1000	Ventana XT; Protease 2 retrieval	Dako, Capinteria, CA
Lambda	Rabbit polyclonal	1:4000	Ventana XT; Protease 2 retrieval	Dako, Capinteria, CA

We report an unusual case of concurrent FL involving lymph nodes, and extranodal MZL involving soft tissue of the chest wall, in a patient with a history of extranodal MZL and CLL/SLL. This case raised the following important considerations: (1) awareness of FL and MZL as a differential diagnostic consideration in atypical lymphoid proliferations showing a nodular/follicular growth pattern; (2) the need for a high index of suspicion in the workup of small B-cell lymphomas with atypical immunophenotypic and cytogenetic features; and (3) consideration of two synchronous processes rather than one process with multisite involvement.

2. Case report

An 82-year-old man presented with unexplained weight loss over a period of 6 months. His past medical history included CLL/SLL in 1997, which was diagnosed on a bone marrow biopsy and confirmed by peripheral blood flow cytometry. In 1999, he was found to have extranodal MZL causing small bowel obstruction, which necessitated segmental resection. He received six cycles of RCHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for advanced stage disease and achieved complete clinical and radiographic remission. The patient also had a history of prostate carcinoma, status post transurethral resection of the prostate, and melanoma and basal cell carcinoma diagnosed on skin biopsies. The prior lymphoma specimens from the outside facility were not available for review or further study.

In 2013, the patient presented with unexplained weight loss without abdominal pain, fevers, night sweats or chills. On physical examination, inguinal lymphadenopathy was detected. A positron emission tomography-computed tomography (PET-CT) scan showed multiple sites of disease: right inguinal lymphadenopathy, masses in the upper abdomen and pelvic sidewall, and a hypermetabolic mass extending from beneath the left clavicle to the base of the left neck. There was no hepatosplenomegaly. An excisional biopsy of a right inguinal lymph node and an incisional biopsy of the left chest wall mass were carried out. Initial morphologic and immunophenotypic analysis led to the diagnosis of extranodal MZL involving both the chest wall and inguinal lymph node. The chest wall mass was associated with extensive amyloid deposition but amyloid was not detected in the lymph node. FISH analysis for *t*(*14*;*18*)/*BCL2* gene rearrangement was performed on the inguinal lymph node and was negative (which was repeated and included an appropriate positive control), which led to additional immunohistochemistry and molecular clonality studies for further workup. These studies confirmed involvement by two separate lymphomas harboring two different B-cell clonal processes, and led to a revised diagnosis of FL in the inguinal lymph node. The patient was treated with 6 cycles of bendamustine and rituximab, which was completed in June 2014. He remains free of clinical evidence of disease at one-year post treatment.

3. Materials and methods

The case was sent in consultation to the Department of Pathology at Stanford University Medical Center. All investigations were carried out with the approval of the Institutional Review Board of Stanford University.

Immunohistochemistry was performed using automated platforms, Ventana XT autostainer, Ventana Medical Systems Inc., Tucson, AZ or Leica Bond-Max autostainer, Leica Microsystems Inc., Buffalo Grove, IL, and included the following markers: CD20, CD79a, CD3, CD5, BCL2, CD10, BCL6, HGAL, LMO2, MNDA, BCL1, IgA, IgG, IgM, and kappa and lambda light chains (Table 1). Polymerase chain reaction (PCR) for B cell clonality was performed as previously described [11]. Flow cytometry was performed at an outside institution and was reviewed.

For FISH, a *BCL2* dual-color breakapart probe (ZytoVision, Bremerhaven, Germany) was used according to methodology that was previously described [12]. PCR was performed using BIOMED-2 primers to detect rearrangements of *IGH* and *IGK*, followed by differential fluorescence detection using GeneScan analysis (Life Technologies, Foster City, CA), as previously described [11]. For detection of *MYD88 L265P* mutation, a single base extension assay using a *MYD88* probe with interrogation of the L265 locus was used [13].

4. Results

Fig. 1 shows representative images of the right inguinal lymph node with effacement of the nodal architecture by back-to-back, variably sized follicles with focal, small, residual germinal centers and attenuated mantle zones. The neoplastic cells, which filled the majority of the nodules, were composed of a monotonous population of small cells with irregular, angulated nuclei. The atypical proliferation was positive for CD20 and BCL2 but lacked CD3, CD5, CD10, BCL1 and SOX11. There was focal BCL6 staining in what appeared to be residual germinal centers, which were also highlighted by Ki-67.