Follicular Lymphoma With Progression to Diffuse Large B-Cell Lymphoma and Concurrent CD5-Negative Mantle Cell Lymphoma-3 Entities in a Lymph Node

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Summary: A 68-year-old woman with a history of follicular lymphoma had pathological findings of grade 3B follicular lymphoma, mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL) identified in 1 lymph node. The DLBCL appeared to be a transformation of the follicular lymphoma. The nodules were diffusely and strongly positive for CD20, BCL6, and BCL2. CD43 highlighted smaller lymphocytes in a fraction of the nodules. BCL1 staining was variable with a mixture of nodular and mantle zone patterns. The diffuse areas showed weaker positivity for CD10, BCL2, and BCL6. CD3 and CD5 highlighted intermixed T cells. The Ki-67 proliferative index was overall estimated to be 60%. Fluorescent in situ hybridization performed on the lymph node was positive for CCND1/IGH. The patterns of BCL1 and BCL6 staining demonstrated 2 separate populations of neoplastic B lymphocytes.

Background
Composite lymphomas (CLs) are an uncommon type of lymphoid neoplasm defined as the coexistence of 2 morphologically and phenotypically distinct types of lymphoid neoplasms occurring in a single site. The identified combinations are varied and can include any combination of Hodgkin lymphoma (HL) with non-Hodgkin lymphoma (NHL) or 2 morphologically distinct types of NHL. One of the most classic, well-recognized CL is Richter syndrome, represented by small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (CLL) and classic HL, or, more commonly, a composite of SLL/CLL and DLBCL. The clonality of the second lymphoma in Richter syndrome has been the focus of many studies because of the insight it provides into lymphomagenesis. The aggressive component of Richter syndrome may be derived from the original neoplastic clone or derived from a second unrelated neoplastic clone. Low-grade NHLs transform into high-grade neoplasms at variable frequency, but this phenomenon usually represents an evolution of the same clonal process. On occasion, 2 distinct diseases can arise from a single clone. A number of so-called “biphenotypic B-cell neoplasms” with 2 phenotypically unrelated malignant populations arising in a patient either synchronous or metasynchronous have been described.

Case Report
Clinical History
A 68-year-old woman noticed an enlarging mass on the right side of her neck. Upon presentation, she was asymptomatic. A surgical excision revealed a 5.4-cm lymph node, which was diagnosed as grade 1 follicular lymphoma. She was followed with close observation. Increasing lymphadenopathy was identified approximately 22 months later, and excisional biopsy of a left axillary lymph node was performed at that time. Tissue sections showed histological evidence of grade 3 follicular lymphoma, DLBCL, and focal MCL. Following the diagnosis of CL, she received 6 cycles with cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab. The patient did well for approximately 15 months before she developed shortness of breath and was found to have a pleural effusion in the right lung. Imaging also revealed extensive lymphadenopathy involving the mediastinum, hilar, and right retrocrural lymph nodes. A significant pleural thickening in the right pleural area and a soft-tissue mass in the right pleura were also identified on imaging. Flow cytometry was performed on the effusion and confirmed the presence of B-cell lympho-
ma. The patient subsequently developed night sweats and lost 25 pounds. She received 2 cycles of benda-
mustine and rituximab but had persistent disease. She continued to require numerous paracenteses and was started on salvage therapy. She died approximately 6 months following the onset of pleural effusions.

Pathological Findings

Review of the hematoxylin and eosin stained sections of the left axillary lymph node biopsy showed that the majority of the lymph node architecture was effaced by a nodular and diffuse infiltrate (Fig 1). The nodular areas were predominantly composed of intermediate- to large-sized lymphocytes with vesicular chromatin, compatible with centroblasts. Intermixed centrocytes were rare. Diffuse areas of centroblasts were also seen (Fig 2). Increased mitotic figures were noted. In addition, nodules of smaller lymphocytes with hyperchromatic chromatin and slightly irregular nuclear contours were found.

Immunohistochemical stains performed on the lymph node showed that CD20 was strongly and diffusely positive in the majority of the lymphocytes. BCL2 was also positive, with stronger staining in the nodular regions. CD43 highlighted mostly smaller lymphocytes in some of the nodules. CD10 and BCL6 highlighted the expanded follicles, with weaker staining in the large cells of the more diffuse areas. BCL1 had variable staining, with a mantle zone pattern in some areas, and a more nodular pattern in others, highlighting the small irregular lymphocytes. BCL6 and BCL1 appeared to be staining 2 separate populations in the nodules (Fig 3). The Ki-67 proliferative index was estimated at approximately 60%. CD3 and CD5 highlighted intermixed T cells. CD5 was negative in the B-cell population.

Fluorescent in situ hybridization studies of the axillary lymph node identified a translocation involving chromosomes 11q13 and 14q32.3 (CCNH/IGH fusion), confirming the presence of MCL. Overall, the lymph node showed DLBCL and grade 3b follicular lymphoma, each comprising approximately 40% of the node; MCL comprised approximately 20% of the node.

Discussion

A review of the literature for coexisting follicular and MCLs revealed approximately 12 reported cases. Most cases described the 2 lymphomas adjacent to each other. One case reported an intermixed pattern of MCL and follicular lymphoma in a patient who had a poor outcome. In addition to follicular lymphoma, MCL has been found to coexist with CLL/SLL, plasma cell dyscrasias, and HL.

MCL is a mature B-cell neoplasm expressing the pan B-cell markers CD19, CD20, CD22, and CD79a, along with the aberrant expression of CD5. MCL usually has a more aggressive clinical course than other small B-cell NHLs. An increased proliferation index usually indicates a more aggressive clinical course in MCL. Our case had a proliferative index of 60%, which is considered high, and the patient had a poor outcome. Our case exhibited an aberrant phenotype in the MCL, lacking CD5, which has been previously re-
Aberrant phenotypes (CD5 negative, CD10 positive, BCL6 positive) may be associated with blastoid and pleomorphic variants of MCL. One review of 25 CD5 negative cases of MCL showed a lymphocytic variant in 20 cases and a blastoid variant in 5 cases. Our case displayed a lymphocytic morphology, and CD10 and BCL6 were negative in the MCL in our case.

Follicular lymphoma usually expresses germinal center cell markers CD10 and BCL6 and antiapoptotic gene BCL2. Follicular lymphoma can be traditionally separated from MCL through the demonstration of a BCL2/IGH rearrangement and a lack of CCND1/IGH rearrangement. MCL colonizing the follicle center will usually express BCL2 by immunohistochemistry, so it is important to perform CCND1 (BCL1) immunohistochemistry, fluorescent in situ hybridization, or both in cases where any concern exists for MCL. A long-term study by Montoto et al showed that, at 10 years, follicular lymphoma transforms to DLBCL in approximately 28% of cases. Advanced-stage and high-risk Follicular Lymphoma International Prognostic Index and International Prognostic Index scores at diagnosis correlate with an increased risk of transformation. Our case demonstrated transformation to DLBCL from the originally diagnosed grade 1 follicular lymphoma in approximately 2 years.

CLs are theorized to represent a more aggressive phase of disease and may have a worse prognosis. Our case had an aggressive clinical course and a poor prognosis following the identification of the CL. As we move toward more personalized medicine, it will be important to recognize these cases, because targeted therapy may improve outcomes. We must also recognize those cases that may require more aggressive therapy. In cases in which clinical findings do not match pathological findings, additional biopsies, including excisional lymph node biopsies, may be necessary to identify areas of transformation or possible CL.

References


