A Unique Composite Follicular Lymphoma and Mantle Cell Lymphoma With a Mixed Cell Pattern and Aggressive Course

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ABSTRACT

Objectives: There are a limited number of reports of composite follicular lymphoma (FL) and mantle cell lymphoma (MCL) in the literature, and all previous cases report that FL and MCL components are separated, even within a single lymph node. Here we report a case of a patient with a distinctive composite FL and MCL with a mixed cell pattern.

Methods: A 34-year-old man presented with left supraclavicular lymphadenopathy for one month. The lymph node contained closely packed nodules of lymphocytes. Immunostaining and fluorescence in situ hybridization demonstrated the FL nature of the Bcl-2– and CD10–positive tumor cells, as well as the scattered cyclin D1–positive MCL tumor cells in the nodules. Double immunohistochemical staining showed an unusual mixed pattern of both types of tumor cells.

Results: The patient received a regimen of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy and achieved partial remission following four cycles of chemotherapy but relapsed one month after the last treatment and died of meninges involvement 8 months after the first presentation.

Conclusions: To our knowledge, this is the first report of composite FL and MCL with a mixed pattern. A mixture of grade IIIb FL and MCL may explain the poor prognosis of the patient.

Composite lymphoma refers to the simultaneous presence of two morphologically and immunophenotypically different lymphomas in the same anatomic site. There are a limited number of reports about composite follicular lymphoma (FL) and mantle cell lymphoma (MCL) in the literature, and all previous cases report that FL and MCL components are separated within a single lymph node. Here we report the case of a young patient with a distinctive composite FL and MCL with a mixed cell pattern. Unlike previous cases, double immunohistochemical staining showed that this patient had an unusual mixed pattern of both types of tumor cells and an aggressive course.

Case Report

Clinical History

A 34-year-old man presented with left supraclavicular lymphadenopathy for 1 month without fever, weight loss, or night sweating. The resected lymph node was 3 × 2 × 2 cm. After the diagnosis of lymphoma, the patient received a regimen of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy and achieved a partial remission following four cycles of chemotherapy but relapsed one month after the last treatment and died of meninges involvement 8 months after the first presentation.

Histologic Findings

H&E staining showed that the lymph node structure was effaced. The lymph node contained closely packed nodules of lymphocytes lacking mantle zones, tingible body
macrophages, and polarity **Image 1A**. Under high magnification, nodules were seen to predominantly comprise large centroblast-like cells, admixed with a few small round lymphocytes **Image 1B**. Centrocytes were sparse within the nodules. No diffuse area of large cells was seen.

Immunohistochemical staining showed that large cells within the nodules were positive for CD20, Bcl-2 **Image 2A**, and Bcl-6 **Image 2B** and that the Ki-67 index was nearly 70%. Large cells were negative for both mum1 and CD3. CD21 staining revealed a network of follicular dendritic cells within the nodules. Based on the morphology and immunostaining results, a diagnosis of FL was made, and the lack of centrocytes in the nodules led to a tumor grading of IIIb.

However, an unexpected finding was the presence of scattered cyclin D1–expressing lymphocytes **Image 2C** within most of the neoplastic nodules but not in the surrounding mantle zones. To confirm the diagnosis, we performed a series of immunostaining procedures. Interestingly, the small cell fraction within the neoplastic nodules was also weakly positive for CD43 **Image 2D** and CD5, consistent with the characteristics of MCL. Next, tumor sections were analyzed by fluorescence in situ hybridization (FISH) employing CCND1-IGH and BCL2-IGH dual-fusion probe sets (Vysis; Abbott Molecular, Abbott Park, IL). Abnormal BCL2-IGH fusion signals were found in 40% of the nuclei scored **Image 3A**, and CCND1-IGH fusions were seen in 15% of the nuclei **Image 3B**. The threshold of positivity for these two FISH assays in our laboratory is 15%. This case was therefore diagnosed as a composite lymphoma, supported by the presence of cyclin D1– and Bcl-2–expressing lymphocyte populations by immunohistochemistry and gene translocation by FISH, the molecular hallmarks of MCL and FL, respectively. To ascertain whether the Bcl-2–positive and cyclin D1–positive lymphocytes derive from the same cell origin, double immunolabeling was performed using the EnVision DuoFLEX Doublestain system (DAKO, Glostrup, Denmark). In this assay, visualization is based on horseradish peroxidase using the 3,3′-diaminobenzidine tetrahydrochloride (DAB) chromogen and alkaline phosphatase using the Fast Red chromogen. Cyclin D1 was stained with DAB (brown), and Bcl-2 was stained with Fast Red (red) **Image 4**, with reciprocal cyclin D1 and Bcl-2 staining performed to confirm the results. We observed that most cells were individually stained with cyclin D1 (brown) or Bcl-2 (red), with less double-positive cells present. Thus, distinct populations of cyclin D1–positive and Bcl-2–positive cells appeared to derive from different clones, consistent with a diagnosis of composite FL and MCL lymphoma with a mixed pattern.

**Discussion**

The incidence of composite lymphomas ranges from 1% to 4.7%, and they occur in patients of both sexes and with a variable age range.4, 6 These lymphomas may or may not be clonally related, with each possibility being reported in the literature,1, 7 and the populations may comprise a combination of two of the following cancers: B-cell (non-Hodgkin) lymphoma, Hodgkin lymphoma, and T-cell lymphoma.8 Composite lymphomas composed of two concurrent, discrete, small B-cell lymphomas have also been described, but these are less common, with MCL rarely forming a component.9

**Image 1** A, The lymph node contained closely packed nodules of lymphocytes lacking mantle zones, tingible body macrophages, and polarity. Inset: Centroblast-like cells (H&E, ×100). B, Nodules were composed predominantly of large centroblast-like cells, admixed with a few small round lymphocytes (H&E, ×400).
MCL and FL are regarded as distinct mature B-cell lymphomas in the World Health Organization 2008 Classification of Tumors of Hematopoietic and Lymphoid Tissue system because of their different morphologic, immunophenotypic, and molecular genetic characteristics, as well as their prognostic implications. They are believed to originate from separate B-cell compartments within the lymph node. If both types of lymphoma develop in the same patient, possibly coexisting in the same lymph node, the tumor is known as a composite MCL and FL.

FLs are usually Bcl-2 positive, CD10 positive, and CD43 negative, and they express the nuclear protein Bcl-6. BCL-2 gene translocation can be detected in most FL cases and can distinguish neoplastic from reactive follicles. In contrast, MCLs are typically CD5 positive and usually CD10 negative and Bcl-6 negative, and virtually nearly all express cyclin D1 and are positive for CCND1 gene translocation. In the present case, both FL and MCL components showed distinctive cell surface antigen expression and molecular genetic alterations that are hallmarks of their respective distinct histogenesis. Specifically, double staining showed that the tumor contained two separate B-cell populations expressing either the cyclin D1 or Bcl-2 antigen characteristic of MCL and FL, respectively, which strongly supports the coexistence of these two distinct lymphomatous components.

Image 2: Immunohistochemical staining showed that large cells within the nodules were positive for (A) Bcl-2 (x200) and (B) Bcl-6 (x400). Scattered cyclin D1–positive lymphocytes (C) were seen in the nodule (x400), and the lymphocytes were also strongly or weakly positive for CD43 (D) (x200).
Composite MCL and FL are extremely rare. Histologically, most reported cases share a common pattern of MCL staining in cells surrounding follicles, as well as in more diffuse areas.\(^1\)-\(^5\) MCL components commonly display a mantle zone growth pattern with diffuse and in situ patterns also observed. Unlike the present case, MCL and FL cells were usually separate in all cases identified by immunohistochemical staining, even in lesions within the same lymph node.\(^1\)-\(^5\) Olsen et al\(^1\) reported a patient with cyclin D1–positive FL, but the cyclin D1–positive cells were actually much less than the Bcl-2–positive cells, which may also represent an example of composite lymphoma of low-grade FL and MCL with a mixed pattern. In our case, double staining showed that MCL and FL cells were mixed together. Grade IIIb FL is an aggressive B-cell lymphoma with a biological behavior resembling that of diffuse large B-cell lymphoma. In addition, MCL is one of the most difficult B-cell lymphomas to treat.\(^10\) Thus, the combination of grade IIIb FL and MCL may explain the poor prognosis of the patient and the poor response to chemotherapy.

Although the initial diagnosis of a composite lymphoma is typically prompted by an observation of morphologic discordance, the increasing use of a wide range of immunophenotypic studies for evaluating lymphomas may lead to more unanticipated findings,\(^11\) as illustrated in this case study. Nevertheless, this case study of an unusual composite lymphoma is unique and of particular interest in that both lymphoma components were mixed together, an observation that has not, to our knowledge, been reported previously.

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References


