Blastic Variant of Mantle-Cell Lymphoma: Cytomorphologic, Immunocytochemical, and Molecular Genetic Features of Tissue Obtained by Fine-Needle Aspiration Biopsy

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Mantle-cell lymphoma (MCL) is a rare type of non-Hodgkin’s lymphoma that has a moderately aggressive clinical course, generally between that of low-grade and of intermediate-grade lymphomas. However, a small subset of MCLs, the so-called “blastic” variant, exhibits a poor prognosis and an aggressive clinical course. We describe a case of blastic MCL that occurred in a 64-yr-old man and that was diagnosed and accurately subclassified as blastic MCL on the basis of a fine-needle aspiration (FNA) biopsy. The aspirate smears showed a monotonous population of intermediate-sized lymphocytes with irregular nuclear contours, finely dispersed nuclear chromatin, and inconspicuous nucleoli. Material was obtained by FNA for ancillary studies (immunocytochemical stains, flow cytometry, cytogenetics, image analysis, and molecular studies) that supported the diagnosis of blastic MCL. Surgical biopsy confirmed the diagnosis. These findings underscore the utility of FNA in diagnosing lymphomas, particularly when the cytomorphologic examination is combined with appropriate ancillary studies. 

Key Words: mantle-cell lymphoma; FNA; cytogenetics

Mantle-cell lymphoma (MCL) is a distinct subtype of non-Hodgkin’s lymphoma, first alluded to by Rappaport1 in 1966 and then more completely described by Berard and Dorfman2 in 1974. Since then, MCL has been known by a number of different names, including intermediate lymphocytic lymphoma, lymphocytic lymphoma of intermediate differentiation, mantle zone lymphoma, and centrocytic lymphoma. Although not originally a part of the Working Formulation, MCL is now recognized as a distinct entity in the Revised European-American Classification of Lymphoid Neoplasms. MCL is thought to represent approximately 2.5% of all non-Hodgkin’s lymphomas. The clinical behavior of MCL is moderately aggressive, with a mean survival of 3–5 yr. Like patients with the low-grade lymphomas of the Working Formulation, patients with MCL may have responses to chemotherapy. However, relapses are common, and the disease is generally progressive.3–14

Although MCL generally exhibits a clinical course similar to that of low- to intermediate-grade lymphomas, a small subset of cases of MCL displays a distinctly more aggressive clinical course. These so-called blastic variants of MCL exhibit a higher mitotic index and are associated with shorter patient survival than conventional MCL.3,7,9 Although the fine-needle aspiration (FNA) cytology of conventional MCL has been described,15–19 the published literature that describes the cytomorphologic features of blastic MCL is limited to 2 cases in which a primary diagnosis of MCL had already been established by surgical biopsy; the patients subsequently developed a body fluid (pleural fluid or cerebrospinal fluid) that was submitted for cytologic evaluation and was found to be positive for blastic MCL.19 Thus, the utility of lymph node FNA for the de novo diagnosis of blastic mantle cell lymphoma is largely unknown.

In this report, we describe a case of blastic MCL in which the primary diagnosis was established on the basis of FNA.

Case Report

History

The patient was a previously healthy 64-yr-old Puerto Rican man who had a 3-mo history of generalized lymphadenopathy, most pronounced in the groin and neck areas. He had also lost 10 pounds over the same 3-mo time period. He sought medical attention in Puerto Rico and underwent an open surgical biopsy of a lymph node in the left side of his
A diagnosis of diffuse, small noncleaved cell lymphoma was rendered. The patient then came to our institution for further evaluation.

When the patient arrived at our hospital, the surgical lymph node biopsy was not available for review. Therefore, an FNA of a 3.0-cm left cervical lymph node was performed in order to confirm the diagnosis prior to treatment. Four separate aspirations were performed using a 23-gauge needle. Air-dried and alcohol-fixed slides were made and stained using the Diff-Quik and Papanicolaou methods, respectively. The needle was rinsed in RPMI tissue culture medium, and a total of 15 million cells was collected, as enumerated with a Coulter counter (Coulter Electronics, Inc., Miami Lakes, FL). The material was divided for flow cytometry, immunocytochemical marking on cytopsin preparations, and gene rearrangement studies. A separate aspirate was obtained for cytogenetic examination in a sterile medium.

**FNA Cytomorphology of Blastic MCL**

The Diff-Quik and Papanicolaou-stained smears revealed a relatively uniform population of intermediate to large lymphoid cells. The nuclei were approximately 4 times larger than a small, mature lymphocyte nucleus. The nuclei had slightly irregular contours and fine, evenly distributed chromatin. Most of the nuclei contained 1–4 small nucleoli. The cytoplasm was scant and stained pale blue on the Diff-Quik stained smears. There were scattered mitoses and apoptotic bodies. Lymphoglandular bodies were present in the background (Fig. 1A,B).

**Immunophenotyping**

Immunophenotyping by both flow cytometry and immunocytochemistry showed a population of B-cells that expressed monoclonal kappa light chain and CD5. Expression of CD23 and CD10 was not observed. Additional markers are summarized in Table I.

**Proliferation Markers**

Flow cytometric DNA ploidy analysis, using the acridine orange method, demonstrated an aneuploid cell population with a DNA index of 1.63, an elevated RNA index of 2.50 (normal = 1.0), and an S + G2M fraction of 28%. DNA ploidy by image analysis also showed an aneuploid population with an elevated proliferation index of 7.2% and with 18.4% of cells with a DNA content >5 c. Additionally, an immunocytochemical stain for Ki-67 revealed a labelling index of 80%. All these findings were consistent with those found with a high-grade lymphoma.20

**Gene Rearrangement Studies and Chromosome Analysis**

Restriction fragment analysis of the DNA extracted from the patient’s cell pellet revealed clonal rearrangement of the immunoglobulin heavy chain gene and germline configuration of the bcl-1 major translocation cluster and bcl-2 major breakpoint region. Similarly, clonal amplification was not
BLASTIC VARIANT OF MANTLE-CELL LYMPHOMA

Fig. 2. Left neck lymph node surgical biopsy. The histologic sections of the excised node demonstrate diffuse effacement by a population of enlarged cells with indistinct cytoplasm, finely dispersed chromatin, and multiple small nucleoli. Mitotic figures are readily identified (hematoxylin-eosin stain, ×800).

detected using consensus JH primers in conjunction with a primer for the bcl-1 major translocation cluster. Cytogenetic analyses of 20 metaphases prepared from colchicine-treated cultured cells showed hypertriploid XXY cells that contained 71–74 chromosomes each. The 20 metaphases examined shared the following cytogenetic abnormalities: +Y, del(1)(p34), −2, del(6)(q21), +10, −11, −13, −14, −15, −17, +18, +20, +21, and +22. A similar cytogenetic profile was observed in cells subsequently harvested from the patient’s bone marrow, which was also diffusely involved by lymphoma.

Surgical Biopsy

After the diagnosis of blastic mantle-cell lymphoma had been established with FNA, the patient’s original surgical biopsy material was obtained from the referring hospital and reviewed. The surgical material showed diffuse effacement of the normal architecture by a monotonous population of enlarged cells with indistinct cytoplasm and finely dispersed chromatin. There were approximately 2 mitotic figures per high-power field (Fig. 2).

Clinical Follow-Up

After the diagnosis of blastic MCL was established, the patient underwent an extensive staging procedure. Bilateral bone marrow biopsies revealed complete involvement of the marrow by lymphoma. There was also evidence of lymphomatous involvement of the spleen, as well as generalized lymphadenopathy. The patient is currently receiving intensive chemotherapy with methotrexate and ara-C.

Discussion

Since its original descriptions in the 1960s and 1970s, MCL has been a controversial disease entity. Also known as intermediate lymphocytic lymphoma, lymphocytic lymphoma of intermediate differentiation, and centrocytic lymphoma, MCL has frequently been diagnostically confused with the low- to intermediate-grade lymphomas of the Working Formulation. Although this confusion and the lack of agreement about the diagnostic criteria of the disease make estimation of incidence difficult, MCL is generally believed to represent about 2.5–5% of all non-Hodgkin’s lymphomas. The blastic variant described in this report is distinctly uncommon, with only a few cases described in the literature. Blastic MCL tends to follow a more aggressive clinical course than conventional MCL, as the median survival of patients with the blastic variant is approximately 3 yr.

While conventional MCL and its blastic variant are uncommon lymphoid malignancies, these neoplasms are associated with some distinct cytomorphologic and immunophenotypic features that are useful to the cytopathologist. Conventional MCL is characterized by a homogeneous population of small- to medium-sized lymphoid cells with scant pale cytoplasm, indented nuclei, dispersed chromatin, and inconspicuous nucleoli. Paraimmunoblasts and transformed cells are absent from conventional MCL, resulting in a monotonous smear. The blastic variant exhibits slightly larger, more irregular nuclei, a more dispersed chromatin pattern, and higher mitotic activity than conventional MCL does, and may frequently be confused with lymphoblastic lymphoma. The patient’s clinical history can be very helpful in making this distinction, because MCL patients are typically older adults, whereas patients with lymphoblastic lymphoma are typically young and present with a mediastinal mass. As in the current case, blastic MCL may also be confused with small noncleaved cell lymphoma, even on histologic sections, because of the monomorphic population of intermediate-sized cells and the increased mitotic activity found with blastic MCL.

Immunophenotypically, MCLs are neoplasms of mature B lymphocytes which typically express the pan-B cell markers CD19 and CD20, as well as monotypic immunoglobulin light chains. In addition, almost all cases of MCL express the pan-T-cell antigen CD5. Although CD10 is variably expressed in MCL, it appears to be absent in the majority of cases. In contrast to B-cell chronic lymphocytic leukemia and nodal small lymphocytic lymphoma, which also aberrantly express CD5, MCL rarely expresses the CD23 antigen. The unique CD5+, CD19+, CD20+, and CD23− immunophenotype of MCL is very useful in distinguishing conventional MCL from other more common low- and intermediate-grade lymphomas by flow cytometry or immunocytochemical techniques; the absence of CD23 distinguishes MCL from small lymphocytic lymphoma/leukemia, and the presence of CD5 distinguishes MCL from follicular center cell lymphoma and marginal zone lymphoma. Because this characteristic immunophenotype is also seen in the blastic variant of MCL, it is also useful in distinguishing
blastic MCL from lymphoblastic lymphoma, large-cell lymphoma, and small noncleaved cell lymphoma.\textsuperscript{3–14}

In addition to its unique immunophenotype, MCL is also distinguished by a characteristic chromosomal translocation.\textsuperscript{8,14,21} This cytogenetic abnormality has been detected in both conventional MCL and blastic MCL.\textsuperscript{22} A chromosomal translocation t(11;14) involving the immunoglobulin heavy chain gene locus on chromosome 14 and the bcl-1 locus on the long arm of chromosome 11 is seen in approximately 60% of MCL cases. This translocation results in overexpression of the cyclin D1 protein, a cell-cycle protein that is not normally expressed at high levels in lymphoid cells. The cyclin D1 protein binds to CdK4 and forms a complex which binds to and phosphorylates the Rb protein. Phosphorylation of Rb triggers the cell to progress from G0/G1 to S, thus driving cellular proliferation.\textsuperscript{14} The increased expression of the cyclin D1 protein in MCL can be demonstrated by in situ hybridization or immunohistochemistry.\textsuperscript{23} Although a bcl-1 translocation was not detected in our case, it should be noted that a bcl-1 rearrangement is present in only 80% of MCL cases.

While the t(11;14) seen in conventional MCL has also been reported in blastic MCL, the full spectrum of cytogenetic abnormalities associated with blastic MCL is not well-characterized because of the rarity of the disease. Haidar et al.\textsuperscript{24} reported a case of blastic MCL which demonstrated a deletion of the long arm of chromosome 12. Deletion of chromosome 12 was not detected in our case, although a markedly abnormal cytogenetic profile was seen. Our findings are similar to those of Tongol et al.,\textsuperscript{25} who have also reported multiple cytogenetic abnormalities in a case of aggressive mantle-cell lymphoma.

The present case illustrates that FNA allows the procurement of ample tissue for the ancillary studies necessary to demonstrate the distinct immunological and proliferative profiles that help diagnose blastic MCL.

References