Blastic Mantle Cell Leukemia: A Previously Undescribed Form

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The leukemic phase of mantle cell lymphoma (mantle cell leukemia) is defined as an absolute lymphocyte count of greater than 4,000/microliter and characterized by the presence of relatively small, slightly irregular lymphocytes in the peripheral blood. Although a variant of mantle cell lymphoma with blastic morphology exists and has been previously well described, a blastic

morphologic variant of mantle cell leukemia has not been described. We report such a case in a 74-year-old male who presented with splenic rupture and an elevated white blood cell (WBC) count. The diagnosis was based on flow cytometric immunophenotyping and the cytomorphology of the peripheral blood. *J. Clin. Lab. Anal.* 13:112–115, 1999. © 1999 Wiley-Liss, Inc.

Key Words: peripheral blood; flow cytometry; immunophenotyping; cyclin D1; bcl-1 gene rearrangement

INTRODUCTION

Mantle cell lymphoma (MCL), previously variously termed lymphocytic lymphoma of intermediate differentiation, centrocytic lymphoma, and mantle zone lymphoma, is a CD5-positive monoclonal B-cell malignancy. It is immunophenotypically differentiated from chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) by the immunophenotypic marker, CD23. This marker is generally positive in SLL/CLL and negative in MCL. This finding has been documented by immunophenotypic studies performed on cell suspensions or frozen sections and in paraffin sections (1–6). In addition, this immunophenotypic differentiation is maintained in distinguishing transformed SLL/CLL from the large cell transformations of MCL (7–8).

At the time of diagnosis of mantle cell lymphoma, peripheral blood involvement may be present—13–21% of cases in most studies (9–12). The leukemic phase of MCL is defined as an absolute lymphocytic count of greater than 4,000/microliter; Shivdasani et al. reported the leukemic phase to be present in 10–20% of patients with MCL (13). In the description of mantle cell leukemia, the cells are small with slightly irregular nuclear membranes. The neoplastic cell population in MCL is generally monotonous and composed of small lymphocytes with variably irregular nuclear membranes. A blastic variant of MCL (MCL-B) has been described in which the neoplastic cell nuclear chromatin is more finely dispersed and there is a high mitotic rate. Although MCL-B may resemble lymphoblastic lymphoma, the nuclear chromatin of MCL-B is slightly more hyperchromatic and the

cell cytoplasm is slightly more abundant than that seen in lymphoblastic lymphoma (14). Although a blastic variant of MCL has been described, to our knowledge, there is no reported case of mantle cell leukemia with blastic morphology.

We report such a case in a 74-year-old male who presented with splenic rupture and “an acute leukemic” blood picture. Flow cytometric immunophenotyping revealed the characteristic immunophenotype of MCL. We describe our findings.

CASE HISTORY

A 74-year-old male presented with generalized weakness, a near-syncope episode, and diffuse abdominal pain of approximately 24-hour duration. On physical examination, he was pale with diffuse abdominal tenderness on palpation. Vital signs revealed a blood pressure of 90/50 mm Hg and a pulse of 68 beats/minute. Initial complete blood count (CBC) at the referring institution reported a white blood (WBC) count of 34,700/ μ L (88% “lymphocytes,” 7% neutrophils, 5% band forms), a hemoglobin (Hgb) of 9.3 g/dL, and a platelet count of 26,000/ μ L. Abdominal ultrasound revealed an enlarged spleen and computerized axial tomographic (CT) scan, a ruptured spleen. Splenectomy was performed and peripheral blood was submitted for flow cytometric immunophenotyping. The clinical impression was “blast crisis of

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chronic myelogenous leukemia." The spleen was described as large, weighing 2,390 grams and measuring 28.0 by 19.0 by 8.0 centimeters, and had a subcapsular infarct. A diagnosis of blastic variant of mantle cell leukemia was rendered. CT scans of chest and pelvis were unremarkable. The patient received six cycles of CVP (Cytoxan, Vincristine, Prednisone) over a five-month period. At last follow-up, the patient was in complete remission.

MATERIALS AND METHODS

Cytomorphology/Immunohistochemistry

A peripheral blood specimen was received for flow cytometric analysis. A Wright's-stained peripheral blood smear was prepared from the flow cytometry specimen. Also received was a hematoxylin-eosin (HE)-stained section of spleen with corresponding paraffin-embedded tissue block. A cyclin D1 stain was performed on the paraffin-embedded tissue block using a cocktail of two antibodies (mouse monoclonal, Immunotech, Margency, France and mouse monoclonal, Nova Castra,

Newcastle Upon Tyne, United Kingdom) and the DAKO LSAB (labelled streptavidin biotin) immunoperoxidase technique with heat-induced antigen retrieval (15). Control tissue was a case of mantle cell lymphoma.

Flow Cytometry

The peripheral blood was analyzed for various antigens on an Ortho Cytofluor absolute flow cytometer (Ortho Diagnostic Systems, Raritan, NJ) using standard techniques and the following commercially available monoclonal antibodies: CD3, CD4, and CD45 (Becton-Dickinson, San Jose, CA); CD5 and CD8 (Gen Trak Inc, Wayne, PA); CD10, CD14 (MY4), CD19, and CD20 (Coulter Clone, Coulter Immunology, Hialeah, FL); HLA-DR (Ortho Diagnostic Systems); and immunoglobulin IgA, IgD, IgG, IgM, and kappa and lambda light chains (Kallestad Inc, Chaska, MA). Dual staining was performed as follows: CD3/4, 19/5, 20/HLA-DR, 14/23, 45/10, kappa/lambda. The other antibodies were singly labeled.

Fig. 1. A Wright's-stained peripheral blood demonstrates the presence of **A**, a large cell with blastic morphology; and **B**, a large cell with coarser chromatin and nucleolus (Wright's stain, $\times 1,000$).

RESULTS

Cytomorphology

Review of the Wright's-stained peripheral blood smear revealed a marked increase in lymphoid cells characterized by irregular nuclear contours and variably condensed nuclear chromatin. Of the lymphoid cells, 43% represented very large cells with blastic morphology, 14% represented intermediate-sized cells, and 43% represented small cells (Fig. 1). HE-stained section of spleen revealed obliteration of the normal splenic architecture by an infiltrate composed of a mixture of lymphoid cells of varying sizes. A large cell component was obvious and associated with a brisk mitotic rate (Fig. 2). There was no distinction between white and red pulp. Cyclin D1 intensely stained the infiltrate.

Flow Cytometry

Flow cytometric analysis of the peripheral blood revealed a WBC of 33,400/ μ L with 57% of cells within a small-to-intermediate-size cell region, 27% within the monocyte region, and 16% within the granulocyte region. Cells within

Fig. 2. Section of spleen reveals a diffuse infiltrate composed of large cells with open chromatin intermixed with small-to-intermediate-sized cells; there is a brisk mitotic rate (Hematoxylin-eosin stain, $\times 1,000$).

the small-to-intermediate-size cell region were composed of only 6% T cells (CD4/CD8 ratio was 0.25) and 80% monoclonal B cells with expression of CD19, CD20, CD24, HLA-DR, aberrant expression of CD5 (Fig. 3), and IgM, kappa of a moderate intensity. There was no coexpression of CD10 or CD23 by the monoclonal B cell population. Cells within the monocyte region were composed of 83% of cells with the same monoclonal B cell immunophenotype. Thus, these monoclonal B cells represented 69% of the peripheral white blood cells. Since 43% of lymphoid cells were blastic by morphology, the blastic lymphoid cells represented 30% (43% of 69%) of the peripheral WBCs.

DISCUSSION

Although a blastic variant of mantle cell lymphoma is well recognized, there are no previous reports describing a blastic variant of mantle cell leukemia. We report such a case of a 74-year-old male who presented with splenic rupture in the setting of splenomegaly and an elevated WBC count with peripheral "blasts." The clinical impression was blast crisis of chronic myelogenous leukemia; flow cytometric immunophenotyping (FCI) was performed on peripheral blood to expedite the diagnosis in this critical clinical setting.

FCI of the peripheral blood was particularly useful, not only in providing expeditious results, but also in defining the cellular origin of the blasts—a mantle cell origin. The blastic morphology was also present in the splenic sections. Cyclin D1 stain subsequently performed on the splenic tissue confirmed the mantle cell origin. BCL1/cyclin D1 rearrangements are associated with cyclin D1 overexpression and

Fig. 3. Flow cytogram of peripheral blood demonstrating dual fluorescence of cells with CD5 and CD19 in the upper right box.

are present in about 70% of mantle cell lymphomas. Cyclin D1 overexpression has a higher specificity (97%) for mantle cell lymphoma (16). Thus, the cyclin D1 overexpression demonstrated in our case supported the immunophenotypic findings. This case illustrates the usefulness of FCI in such cases and a previously undescribed form of mantle cell leukemia.

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