Diffuse Large Cell Lymphoma of B-Cell Type Associated with Reactive Hemophagocytosis*

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ABSTRACT

Some lymphomas, virtually all phenotypically of the T-cell type, have been associated with the phenomenon of hemophagocytosis. Only two B-cell lymphomas, one T-cell-rich and the other an angiocentric lymphoma, have been observed to exhibit this phenomenon. A case is reported of a diffuse large cell lymphoma of the B-cell type associated with reactive hemophagocytosis. Cytokines or other humoral factors produced by the lymphoma are a possible cause, and their effect is probably systemic. There is some evidence suggesting correlation of hemophagocytosis with tumor aggressiveness.

Introduction

Reactive hemophagocytosis by histiocytes may occur as a result of benign or malignant conditions. Benign conditions include infections caused by a number of viruses, mainly of the herpes family by both Gram-positive and negative bacteria, fungi, and protozoa. In addition, autoimmune diseases can be associated with this condition, as can immune-suppressed states and drug therapy (as with phenytoin). Malignant conditions include neoplasms such as non-Hodgkin’s lymphoma, Hodgkin’s disease, multiple myeloma, acute lymphoblastic and myeloid leukemias, chronic lymphocytic and hairy cell leukemia, and carcinoma of the stomach and ovary. However, the phenomenon of hemophagocytosis has rarely been observed in B-cell lymphomas. A case is reported of a diffuse large B-cell lymphoma in which hemophagocytosis was prominent in bone marrow, spleen, and lymph nodes.

Case Report

A 43-year old male presented with splenomegaly and generalized lymphadenopathy of three months duration. Biopsy of inguinal lymph nodes showed B
cell lymphoma of the diffuse large cell type. A staging bone marrow biopsy was negative. Chemotherapy was administered, and splenectomy was performed eight months later for thrombocytopenia. Histological examination of the spleen showed a lymphoma of the same type. Repeat bone marrow biopsy performed nine months after the initial diagnosis showed no evidence of lymphoma.

Histopathology of both the inguinal node and spleen showed diffuse infiltration of large lymphoid cells with large nuclei, prominent nucleoli, and moderate amount of cytoplasm. Frequent mitotic figures were present. The tumor cells were strongly positive for the specific B-cell marker, L26 (CD 20), and were negative for CD3, a T-cell marker. They were also negative for CD43, a myeloid cell marker, and bcl-2, a follicular lymphoma marker. These results are summarized in table I. Present in both inguinal nodes and spleen were numerous histiocyes, many of which exhibited erythrophagocytosis and leucophagocytosis as shown in figure 1 (A and B). Histiocytic hemophagocytosis was also observed in the bone marrow aspirates (figure 1C) performed in the staging procedure, even though there was no evidence of lymphoma on both the bone marrow aspirates and biopsies. From the histopathological pattern and the results of the marker studies, this lymphoma was categorized as diffuse, large B-cell lymphoma, according to the Revised European-American Lymphoma (REAL) classification.2

Discussion

Almost all cases of non-Hodgkin's lymphoma associated with reactive hemophagocytosis have been of T-cell origin. A report by Jaffe et al3 included six patients with T-cell lymphoma, two of them with the peripheral T-cell type. All of these patients had short survivals. Falini et al4 presented nine patients with peripheral T-cell lymphoma associated with reactive hemophagocytosis. Seven of them had short survivals, one had complete remission, and one survived a relapse. Gonzalez et al5 described six patients with T-cell lymphoma localized primarily to subcutaneous tissue and associated with hemophagocytosis. Five of the six were fatal. Wong et al6 described hemophagocytosis in four patients with Ki-1 anaplastic large cell lymphoma. All these patients presented with bone marrow involvement, an uncommon observation in this type of lymphoma.

To date, only two reported cases have been found of B-cell lymphomas associated with reactive hemophagocytosis: one, associated with a T-cell-rich B cell lymphoma,7 and the other associated with an angiotropic B-cell lymphoma, a rare lymphoma in which the malignant cells occur predominantly in blood vessels with minimal lymph node involvement,8 unlike the case reported here. In lymphomas in which it has been

<table>
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<th>Histologic Features</th>
<th>CD3 (T)</th>
<th>L26 (CD 20) (Mature B)</th>
<th>Leu 22 (CD43) (Myeloid, T,B Subset)</th>
<th>BCL2 Follicular Lymphoma (T/B Subset)</th>
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<tr>
<td>Large lymphoid cells, Large nuclei, Prominent nucleoli, Moderate cytoplasm, Frequent mitotic figures, Present in lymph nodes, spleen, and bone marrow</td>
<td>-</td>
<td>+</td>
<td>b</td>
<td>-</td>
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* T and B in parenthesis refer to B–cell and/or T–cell markers.

b Small lymphocytes were immunopositive.
FIGURE 1. (A) Histiocytic hemophagocytosis in inguinal lymph node; (B) spleen; and (C) bone marrow aspirate. In each figure, the phagocytic cell is shown with an arrow.
documented, reactive hemophagocytosis was probably caused by the cytokines produced by lymphoma cells leading to activation of histiocytes. In the case reported by Domman-Scherrer et al., the phenomenon followed administration of granulocyte-macrophage colony stimulating factor (GM-CSF) for chemotherapy-induced granulocytopenia, suggesting a possible role of endogenous GM-CSF. A 50 kd phagocytosis-inducing protein has been isolated from the supernatants of lymphoma cell cultures from patients with angiocentric T-cell lymphomas. However, specific cytokines that may induce hemophagocytosis in B-cell lymphomas have not been identified.

Viral infections have also been implicated in some cases of hemophagocytosis. In these cases, the hemophagocytosis is transient, whereas in cases of lymphoma with reactive hemophagocytosis, the hemophagocytic histiocytes are intermingled with the lymphoma cells.

In the present case, there was no evidence of infection, and the hemophagocytosis that was observed occurred in biopsies performed nine months apart. In both biopsies, hemophagocytic histiocytes were found among malignant cells in lymph nodes. Also, as already noted, bone marrow and spleen involvement were observed. A similar distribution has also been reported by Jaffe et al. Our parallel findings may, therefore, imply that the observed hemophagocytosis may have been caused by unidentified cytokines, which exert a systemic effect.

Acknowledgment

Thanks are extended to the staff pathologists at Brooklyn Veterans Affairs Medical Center (BVAMC) who issued the diagnoses and the staff of the Medical Media Service at BVAMC who prepared the photomicrographs.

References