Sinus Histiocytosis with Massive Lymphadenopathy Associated with Malignant Lymphoma

Hirofumi SHODA, Teruaki OKA*, Morihiro INOUE, Seishi KUSAKA, Hideo TSUNEYOSHI, Jun MIYAZAKI and Shinji SUNAGA

Abstract

Sinus histiocytosis with massive lymphadenopathy (SHML) is a distinct benign clinicopathological entity, characterized by painless enlargement of lymph nodes due to sinus histiocytosis. Here, we report a case of SHML with diffuse large B-cell lymphoma. A 64-year-old man was admitted to our hospital because of fever. He presented with enlargement of a small cervical lymph node and huge abdominal paraaortic lymphadenopathy. Cervical lymph node biopsy revealed SHML and bone marrow biopsy showed infiltration of large B-cell lymphoma. Several cases of SHML associated with lymphoma have been documented to date, but this type of simultaneous occurrence has not yet been reported. (Internal Medicine 43: 741–745, 2004)

Key words: sinus histiocytosis, malignant lymphoma, immunohistochemistry

Introduction

Sinus histiocytosis with massive lymphadenopathy (SHML) was first described as a distinct clinicopathological entity by Rosai and Dorfman in 1969 (1). SHML is commonly characterized by painless cervical lymphadenopathy, and its clinical course is generally benign and self limiting. One of the microscopic features of lymph nodes in SHML is the expansion of lymph node sinuses with numerous histiocytes that sometimes show emperipolesis of lymphocytes. Immunohistochemical studies reveal that such histiocytes are positive for the S-100 protein, a common marker of Langerhans cell histiocytosis, and negative for CD1a (2). Histiocytes in SHML are considered reactive macrophages (3, 4).

Several cases in which SHML and malignant lymphoma developed in the same patient were previously reported (5–12). In a review of 423 cases entered in the SHML Registry, only four were identified as concurrent cases of lymphoma (13). Here we describe a new case of SHML associated with malignant lymphoma. In this case, SHML and malignant lymphoma occurred simultaneously in different anatomical sites: the former was noted in the cervical lymph node and the latter in the bone marrow. Although the cause of SHML is still unknown, we presumed that the pathogenesis of SHML in our case may be associated with malignant lymphoma.

Case Report

A 64-year-old Japanese man was admitted to our hospital in June 2002 with a 2-week history of fever, body weight loss, night sweat and general fatigue. He had been healthy and an annual medical checkup performed 2 months before had shown normal results. On admission, physical examination revealed fever and a 1-cm enlargement of a left cervical lymph node. Other superficial lymph nodes were not enlarged, and there were no skin eruptions. His leukocyte count was 6,100/μl, including immature myeloid cells and erythroblasts (leukoerythroblastosis). Mild anemia was also detected (Hb 11.0 g/dl). The erythrocyte sedimentation rate (ESR) was more than 115 mm/h. Serum lactate dehydrogenase (LDH) and soluble interleukin 2 receptor (sIL2R) levels were markedly increased (LDH, 1,652 IU/l; sIL2R, 12,300 U/ml). Hypergammaglobulinemia was not noted. Antibodies to human T cell leukemia virus 1 and human immunodeficiency virus were not examined. Chest CT showed a normal lung field with no mediastinal lymphadenopathy. Abdominal CT revealed hepatospleno-
megaly and a large lymphadenopathy in the paraaortic area, causing bilateral hydronephrosis. Gastrofiberscopy and colonoscopy gave normal findings.

We suspected lymphoma and performed biopsy of the cervical lymph node. Microscopic examination revealed that numerous histiocytes with abundant pale cytoplasm had invaded the lymph sinuses (Fig. 1). Occasionally, engulfed lymphocytes were noted in the cytoplasm of the histiocytes. Immunological staining showed that the invading histiocytes were positive for CD68 and the S-100 protein, and negative for CD1a and CD20 (Fig. 2). These findings were consistent with the features of SHML. Epstein-Barr virus-encoded RNA (EBER) was negative in the histiocytes, as examined by in situ hybridization. No lymphoma cells were noted in the cervical lymph node. Bone marrow biopsy showed diffuse infiltration of large atypical lymphocytes, which were positive for CD20 and CD79a, and negative for CD3 (Fig. 3). Flow cytometric analysis proved inadequate because bone marrow cells were not sufficiently aspirated. Karyotypic analysis revealed a normal karyotype. No hemophagocytic cells were noted in the bone marrow. We finally diagnosed the patient as having SHML involving the cervical lymph node and diffuse large B-cell lymphoma (DLBL) infiltrating the bone marrow. Abdominal lymph nodes were not biopsied because high fever persisted after admission, deteriorating his performance status.

The present patient was treated with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). Soon after starting the chemotherapy, fever subsided and the levels of LDH and sIL2R decreased. CT after four cycles of CHOP chemotherapy revealed a persistent abdominal mass, although the size of the mass decreased. Two additional cycles of salvage chemotherapy, consisting of carboplatin, cytarabine, etoposide, and mitoxantrone, were given and thereafter an uncertified complete remission was finally achieved.

Discussion

Here, we describe the first case in which SHML and malignant lymphoma occurred simultaneously in different anatomical sites: the former was noted in the cervical lymph node and the latter in the bone marrow. Lymphoma cells in the present patient expressed a B-cell phenotype, although the immunophenotypic characterization was not sufficient. Because the lymphoma cells were large, we diagnosed the lymphoma in our patient as DLBL according to the WHO classification (14). It was unknown whether the abdominal lymph nodes were involved in lymphoma or SHML. SHML.

Figure 1. Biopsy specimen of a cervical lymph node. (A) Lymph node sinuses were expanded (HE stain, ×40). (B) Higher magnification showed infiltration of histiocytes (HE stain, ×400). An engulfed eosinophil was noted (arrowhead).
rarely responds to chemotherapy (15), but in our patient the enlargement of abdominal lymph nodes decreased following chemotherapy. Therefore, we considered that abdominal lymphadenopathy may have been caused by the lymphoma.

SHML sometimes shows immunologic abnormality (6). To date, four cases have been reported in which SHML preceded lymphoma (5–8). In these cases, an immune dysfunction caused by SHML may have induced the development of lymphoma. However, it seemed unlikely that our case had a longstanding history of SHML before the development of the lymphoma because his laboratory tests performed 2 months before admission showed normal results.

Previously, eight cases showing the simultaneous occurrence of lymphoma and focal SHML in the same lymph node were reported (10–12). In these cases, it was postulated that the SHML lesion may have appeared in association with lymphoma. Another setting of histiocytic reaction to lymphoma is lymphoma-associated hemophagocytic syndrome (LAHS) (16). Hemophagocytic syndrome is caused by the abnormal activation of macrophages, resulting in pancytopenia due to the phagocytosis of blood cells. Although the mechanism underlying macrophage activation remains unknown, hemophagocytic syndrome certainly occurs in some patients with malignant lymphoma, and the concept of LAHS is definitely established. As in the case of LAHS, we assumed that SHML may be associated with malignant lymphoma in our patient.

Epstein-Barr virus (EBV) infection is also considered as one of the causes of hemophagocytosis, that is, virus-associated hemophagocytic syndrome (VAHS). Thus, hemophagocytic syndrome is considered as a reactive histiocytosis to various disorders such as malignant lymphoma and viral infection. Similarly, SHML may be caused by the abnormal activation of macrophages due to lymphoma or infection. Indeed, viral infections, particularly those by EBV and human herpesvirus 6 (HHV6), are suggested to be one of the causes of SHML (17, 18). In our patient, EBER was negative; unfortunately, we did not examine viral antigens and antibodies to EBV or HHV6.

The mechanism underlying macrophage activation has not yet been elucidated in SHML. Maia et al postulated that B-cell-derived cytokines may induce the development of SHML (12). On the other hand, Middel et al suggested that stimulation of monocytes or macrophages by a macrophage colony-stimulating factor represents the main mechanism underlying the pathogenesis of SHML (4). Further investigations are necessary to clarify the role of cytokines in the development of SHML.
References


