Sinus Histiocytosis with Massive Lymphadenopathy and Malignant Lymphoma Involving the Same Lymph Node: A Report of Four Cases and Review of the Literature

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Sinus histiocytosis with massive lymphadenopathy (SHML), also known as Rosai-Dorfman disease, is a disorder of unknown cause. Rarely, patients with SHML also have malignant lymphoma, usually involving anatomic sites different from those involved by SHML. We report four patients in whom SHML and malignant lymphoma were identified in the same lymph node biopsy specimen. The SHML in each case was present as a small focus, less than 1 cm. Immunohistochemical studies showed that the abnormal histiocytes were positive for S-100 and negative for CD1a. The malignant lymphomas included two cases of follicular lymphoma and two cases of Hodgkin's disease, nodular lymphocyte predominant type. The presence of SHML in these patients did not impact clinical decisions, and there was no evidence of SHML elsewhere. Thus, the presence of focal SHML associated with malignant lymphoma in these cases was an incidental histologic finding that seems not to have had any clinical significance.

KEY WORDS: Hodgkin's disease, Immunohistochemistry, Non-Hodgkin's lymphoma, Rosai-Dorfman disease, Sinus histiocytosis with massive lymphadenopathy.

Sinus histiocytosis with massive lymphadenopathy (SHML), first described by Rosai and Dorfman (1) as a distinct clinicopathologic entity in 1969, is a non-neoplastic, usually self-limiting disease of unknown cause. SHML most commonly presents as painless cervical lymphadenopathy, with frequent involvement of other lymph node groups. In 30% of patients, extranodal sites are involved, such as skin, bone, and breast (1–4). Accompanying clinical and laboratory findings include fever, leukocytosis, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia (3). Although fatalities in patients who have SHML rarely have been reported, particularly in patients who have immunologic abnormalities (3, 5), most patients who have SHML follow a benign clinical course, often with spontaneous resolution of disease.

The association of SHML with Hodgkin's disease or non-Hodgkin's lymphoma is rare; nine such cases have been reported in the literature (5–11). Of these, only four patients had SHML and malignant lymphoma involving the same lymph node simultaneously (10, 11). In all four cases, the SHML was associated with Hodgkin's disease. We report four additional cases of focal SHML present in lymph nodes also involved by malignant lymphoma, two Hodgkin's disease and two follicular lymphoma.

MATERIALS AND METHODS

Four cases of focal SHML associated with malignant lymphoma were retrieved from the files of the Division of Pathology, University of Texas M.D. Anderson Cancer Center. All hematoxylin-eosin– and immunoperoxidase-stained histologic slides of the lymph node specimens were examined for this study. The malignant lymphomas were classified according to the revised European-American classification of lymphoid neoplasms (12). Clinical history and follow-up information were obtained from hospital records and contact with the patients' physicians.

Immunohistochemical studies were conducted using fixed, paraffin-embedded tissue sections and the LSAB2 detection system (Dako, Carpinteria, CA). To assess the neoplastic component, the following monoclonal antibodies with their corresponding dilutions were used in one or more cases:

CD20 (1:700), CD3 (1:500), CD30 (1:40), CD45 (1:300), CD57 (1:100), and EMA (1:30) (Dako); and CD15 (1:100) (Becton-Dickinson, San Jose, CA). To assess the histiocytes of the SHML component, in every case, antibodies specific for S-100 protein (polyclonal, 1:1000 dilution; Dako) and CD1a (monoclonal, 1:1000 dilution; Immunotech, Westbrook, ME) were used.

RESULTS

Clinical Findings

The clinical features of the four cases are summarized in Table 1, and their case histories are briefly reported here.

Case 1

A 62-year-old Hispanic woman from Venezuela presented in April 1998 with a 2-week history of enlarged cervical lymph nodes and no other symptoms. She denied fever, weight loss, and night sweats. Physical examination revealed generalized lymphadenopathy (bilateral occipital, axillary, inguinal, and left scapular lymph nodes) and hepatosplenomegaly. The inguinal lymph nodes were largest, 3 cm bilaterally. Laboratory studies showed mild pancytopenia but no other abnormal findings. An excisional biopsy of the left inguinal lymph node showed both SHML and follicle center lymphoma, follicular, Grade 2. Bone marrow biopsy showed paratrabecular lymphoid aggregates of low-grade lymphoma. Thus, the patient's disease was at Ann Arbor Stage IVA. The patient was treated with two cycles of fludarabine with significant resolution of lymphadenopathy. She returned to Venezuela in June 1998 and continued fludarabine therapy under the care of her local physician.

Case 2

A 44-year-old black woman developed right axillary lymphadenopathy (4 cm) in 1984, at 30 years of age. Excisional biopsy revealed both SHML and Hodgkin's disease, nodular lymphocyte predominant type, with diffuse areas, the latter suggesting onset of transformation. She reported no symptoms and denied fever, weight loss, and night sweats. Staging studies showed that the neoplasm was limited to the right axilla and was therefore Ann Arbor

Stage IA. She was treated with local irradiation and underwent complete remission.

In July 1997, the patient developed deep venous thrombosis of the right leg. At that time, an abdominal CT scan revealed a 13-cm mass, which was biopsied and shown to be diffuse large B-cell lymphoma (CD20 positive, CD30 positive, CD3 negative). There was no histologic evidence of SHML. Clinical Ann Arbor stage at that time was IIIB. The patient was treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for eight cycles. She achieved complete clinical remission in March 1998. Subsequently, the patient developed doxorubicin-induced cardiotoxicity followed by relapse of lymphoma in the liver and retroperitoneal lymph nodes. In September 1998, the patient came to M.D. Anderson Cancer Center to be considered for bone marrow transplantation. A week later, before any additional treatment, the patient died of pneumonia and sepsis.

Case 3

A 28-year-old black man, with a history of venous stasis ulcers of the right leg, had painless swelling of a left cervical lymph node (4 cm) that had been gradually increasing in size during the previous 3 to 4 years. He denied fevers, weight loss, and night sweats. In July 1998, the patient decided to have the lymph node excised because it was physically visible. The lymph node biopsy specimen was involved by both SHML and Hodgkin's disease, nodular lymphocyte predominant type. Physical examination revealed a 2-cm lymph node in the left axilla. All staging studies were negative, and thus the disease was Ann Arbor Stage IIA. The patient was treated with local irradiation (39.6 Gy in 22 fractions) and is in complete remission without symptoms.

Case 4

A 63-year-old white woman presented in 1976, at age 46 years, with arthralgia, sweats, fatigue, and significant abdominal pain. These symptoms progressed until August 1977 when the patient underwent laparotomy and was found to have diffuse mesenteric lymphadenopathy. Biopsy of a mesenteric lymph node revealed non-Hodgkin's lymphoma, interpreted elsewhere as diffuse mixed small and large cell of B-cell lineage (slides not

TABLE 1. Clinical and Histologic Findings

Case	Age/Sex/Race	LN Site	ML	SHML Size	ML Stage	Therapy for ML
1	62/F/Hispanic	L inguinal	FCL-F, Grade 2	8 mm	IVA	Fludarabine
2	30/F/Black	R axillary	HD, N+D-LP	2 mm	IA	Local XRT
3	28/M/Black	R cervical	HD, N-LP	2 mm and 3 mm	IIA	Local XRT
4	63/F/White	L inguinal	FCL-F, Grade 1	6 mm	IIIB	Total nodal XRT

LN, lymph node; ML, malignant lymphoma; SHML, sinus histiocytosis with massive lymphadenopathy; FCL-F, follicle center lymphoma–follicular; HD, Hodgkin's disease; N, nodular; D, diffuse; LP, lymphocyte predominant; XRT, radiation therapy.

available for review). Physical examination and staging studies showed Ann Arbor Stage IIIB disease. She was treated with CHOP for six cycles, followed by chlorambucil for 7 additional months, and achieved complete clinical remission. However, within months, the patient relapsed and was treated with nine cycles of nitrogen mustard, vincristine, procarbazine, prednisone.

In 1992, she developed myalgia, fatigue, and night sweats, but no fever, of 9 months duration. At that time, physical examination revealed an enlarged left inguinal lymph node but no other lymphadenopathy. Excisional biopsy of the inguinal lymph node revealed both SHML and follicle center lymphoma, follicular, Grade I. After total nodal radiation therapy, the patient's symptoms disappeared and she was in complete clinical remission at last follow-up, 3 years later (Fig. 1).

Pathologic Findings

The diagnosis of malignant lymphoma in all four cases was established using histologic criteria and was supported by immunohistochemical data.

In Cases 1 and 4, the lymph node architecture was subtotally replaced by numerous follicles composed of small cleaved and large lymphoid cells. In Case 1, the follicles were a mixture of small cleaved and large cells. In Case 4, small cleaved cells predominated (Fig. 1). Immunohistochemical studies showed that the neoplastic cells were positive for CD20 and BCL-2 and were negative for CD3. Thus, these neoplasms were classified as follicle center lymphoma, follicular, Grade 2 (Case 1) and Grade 1 (Case 4).

In Cases 2 and 3, the lymph node architecture was replaced by vaguely nodular neoplasms, with diffuse areas in Case 2. The nodules were composed of numerous small, round lymphocytes and histiocytes and occasional large lymphoid cells with multilobated nuclear contours consistent with L&H (lymphocytic and/or histiocytic) variants. Immunohistochemical studies showed that the L&H variants in both cases were strongly positive for CD20 and EMA and negative for CD3, CD15, and CD30. CD57-positive small lymphocytes were increased within the nodules, and foci of satellite formation by CD57-positive cells around the L&H cells were also identified. Thus, both neoplasms were classified as Hodgkin's disease, nodular lymphocyte predominant, with diffuse areas suggestive of onset of large cell transformation in Case 2.

In each lymph node biopsy specimen, foci of SHML were identified within sinuses and between the neoplastic nodules in one or multiple areas. In these foci, aggregates of large histiocytes with abundant pale cytoplasm and lymphophagocytosis (emperipolesis) associated with mature plasma
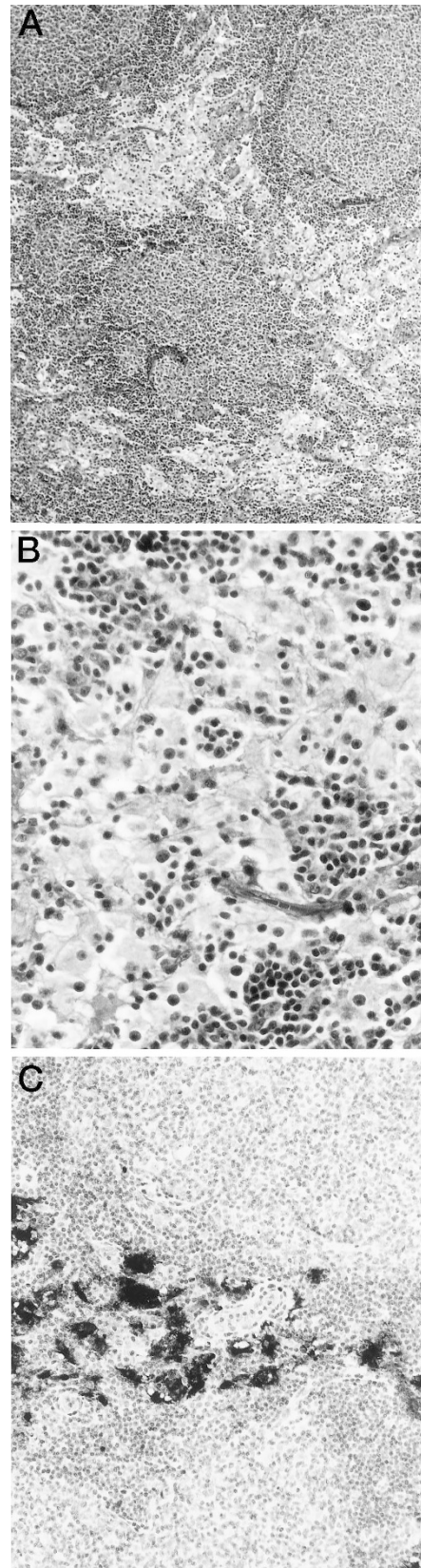
FIGURE 1. Follicle center lymphoma, follicular, Grade 1 (Case 4). **A**, focus of sinus histiocytosis with massive lymphadenopathy (SHML) is present between neoplastic follicles (hematoxylin and eosin, 100×). **B**, the SHML histiocytes had central nuclei and abundant pale cytoplasm with emperipolesis (hematoxylin and eosin, 400×). **C**, the SHML histiocytes were strongly positive for S-100 protein and were negative for CD1a (not shown) (immunohistochemistry with hematoxylin counterstain, 200×).

TABLE 2. Sinus Histiocytosis with Massive Lymphadenopathy and Malignant Lymphoma Involving Different Anatomic Sites

Reference	Age/Sex	NHL	Anatomic Sites	Time Interval Between SHML and NHL
Foucar *et al.*, 1984 (5)	6/M	Large cell immunoblastic	Cervical, axillary LN (SHML); central nervous system (NHL)	ML 8 mo after SHML
Rangwala *et al.*, 1990 (6)	62/M	Small noncleaved	Inguinal LN (SHML); palate, kidney (NHL)	ML 4 y after SHML
Koduru *et al.*, 1995 (7)	52/M	T-cell	Supraclavicular LN (SHML); cervical LN (NHL)	ML 8 y after SHML
Krzemieniecki *et al.*, 1996 (8)	17/F	High grade, NOS	Cervical LN (SHML); axillary LN (NHL)	ML 5 y after SHML
Lossos *et al.*, 1997 (9)	67/M	Small lymphocytic	Spleen (NHL); testis, kidney (SHML)	ML 12 y before SHML

NHL, non-Hodgkin's lymphoma; SHML, sinus histiocytosis with massive lymphadenopathy; LN, lymph node; NOS, not otherwise specified; ML, malignant lymphoma.

cells were present. The histiocytes in all four cases displayed strong positivity for S-100 protein and were negative for CD1a.

In each case, SHML was present as small foci of variable size in two dimensions. In Case 1, there was a single 8-mm focus. In Case 2, a single 2-mm focus was identified. In Case 3, two SHML foci were seen, 3 mm and 2 mm, respectively. In Case 4, the focus of SHML was 6 mm (Fig. 1). In all cases, the SHML occupied less than 10% of the total lymph node tissue examined histologically.

DISCUSSION

The association between SHML and malignant lymphoma is rare. A MEDLINE search of the literature identified nine reported cases (Tables 2 and 3). Five patients had SHML and non-Hodgkin's lymphoma that developed at different times and involved different anatomic sites (Table 2). In four of these patients, SHML preceded malignant lymphoma by 1 to 8 y (5–8). The other case developed extranodal SHML 12 y after cure of small lymphocytic lymphoma (9).

Of the remaining four previously reported cases of SHML and malignant lymphoma (Table 3), SHML was present in lymph node biopsy specimens also involved by lymphoma (10, 11). In each case, the SHML was focal and was an incidental finding in a lymph node specimen that otherwise was involved by Hodgkin's disease: nodular lymphocyte predominant in two cases, mixed cellularity in one case, and unclassified in one case. In one of these patients, SHML initially was observed 7 y before the diagnosis of Hodgkin's disease, nodular lymphocyte predominant (11). Subsequent biopsy of the same anatomic site showed coexistent SHML and recurrent Hodgkin's disease.

In this study, we describe four additional cases of malignant lymphoma and focal SHML simultaneously present in the same lymph node biopsy specimen. Two cases had low-grade follicular lymphoma, and to our knowledge, these represent the first reported examples of SHML and non-Hodgkin's lymphoma in the same lymph node. The other two cases were SHML coexistent with Hodgkin's disease, nodular lymphocyte predominant type, similar to cases previously reported by others (10, 11).

Although the four cases we report had only small foci of SHML, histologic and immunohistochemical features that are characteristic of SHML were present. There were clusters of large histiocytes with abundant pale cytoplasm demonstrating emperipolesis. Immunohistochemical studies showed that the histiocytes were positive for S-100 and negative for CD1a as expected. It is known that the SHML cells share several markers with the cells of Langerhans' cell histiocytosis, such as S-100 (13, 14). However, SHML cells generally do not express CD1a, which is normally expressed by Langerhans' cells (15).

Table 3 summarizes the four cases we describe as well as the four previously reported cases of SHML and malignant lymphoma involving the same lymph

TABLE 3. Coexistent Sinus Histiocytosis with Massive Lymphadenopathy and Malignant Lymphoma Involving the Same Lymph Node

Reference	Age/Sex	Type of ML	LN Site
Falk *et al.*, 1991 (10)	49/M	HD, MC	Retroperitoneal
	24/M	HD, NOS	Cervical
Maia *et al.*, 1995 (11)	39/M	HD, N-LP	Cervical
	11/M[a]	HD, N-LP	Axillary
Present study	62/F	FCL-F, Grade 2	Inguinal
	30/F	HD, N+D-LP	Axillary
	28/M	HD, N-LP	Cervical
	63/F	FCL-F, Grade 1	Inguinal

ML, malignant lymphoma; LN, lymph node; HD, Hodgkin's disease; MC, mixed cellularity; NOS, not otherwise specified; N, nodular; LP, lymphocyte predominant; FCL-F, follicle center lymphoma, follicular; D, diffuse.

[a] Focal SHML was also noted previously at age 4 in inguinal lymph node.

node. Six patients (75%) had Hodgkin's disease, including four lymphocyte-predominant and two mixed cellularity. Although the possibility of coincidental occurrence cannot be excluded, the coexistence of malignant lymphoma and SHML in the same lymph node suggests a possible link in the pathogenesis of those diseases. This link seems particularly likely for nodular lymphocyte-predominant Hodgkin's disease, considering the relative rarity of this neoplasm.

The cause and pathogenesis of focal SHML associated with malignant lymphoma in these four cases are unknown. The histiocytes of SHML are polyclonal, as shown by others using molecular methods and the HUMARA technique (16). Some studies have suggested that human herpesvirus (HHV)-6 may play a role in the pathogenesis of SHML. HHV-6 is a ubiquitous virus that infects most individuals in childhood and remains latent in host cells; infection can be reactivated by immunodeficiency (17, 18). HHV-6 causes exanthem subitum (sixth disease) in children and hepatitis, encephalitis, and opportunistic infections in patients who have acquired immunodeficiency syndrome and in transplant recipients. Levine *et al.* (17) detected HHV-6 DNA by *in situ* hybridization in seven of nine SHML cases. In another case of SHML that initially presented as giant granuloma annulare, HHV-6 was detected by Southern blot hybridization (19). HHV-6 in SHML also seems to be functionally active as Luppi *et al.* (20) have shown HHV-6 antigen expression by the abnormal histiocytes, further suggesting an causative role for the virus.

Patients who have SHML commonly have immunologic abnormalities (5). Possibly, the foci of SHML in the four cases we report are related to immunodeficiency associated with the presence of malignant lymphoma, which predisposed to reactivation of HHV-6 infection. However, whether HHV-6 directly causes SHML or is only an innocent bystander is not known. Alternatively, SHML may be a specific immune response to the presence of malignant lymphoma. Similar mechanisms, although not specifically involving HHV-6, have been postulated by others to explain the analogous situation of Langerhans' cell histiocytosis coexistent with malignant lymphoma (21).

Serologic evidence of Epstein-Barr virus (EBV) infection has been documented in many SHML patients, especially in patients with associated immune disorders (3). It is also conceivable that SHML could result from EBV infection, either by directly infecting histiocytes or from an aberrant histiocytic response-associated infection of other cells. Studies do not favor the former hypothesis, as EBV is rarely detected in SHML tissues. Levine *et al.* (17) detected EBV DNA by *in situ* hybridization in only one of nine SHML cases. Similarly, Tsang *et al.* (22) did not detect EBV in five SHML cases analyzed. Therefore, EBV is probably not the causative agent of SHML. However, SHML could still represent an aberrant histiocytic response to EBV infection. A similar phenomenon is seen in reactive and tumor-associated hemophagocytic syndromes, in which EBV can be detected in reactive or neoplastic lymphoid cells but not in histiocytes, suggesting that the histiocytic proliferation is a reaction related to the presence of EBV infection (23). Unfortunately, serologic studies for EBV infection were not conducted in the patients we report.

The patients in this study did not have evidence of SHML in other nodal or extranodal sites, and there were no clinical manifestations suggestive of fully developed SHML. The foci of SHML were small (<1 cm) and occupied less than 10% of the lymph node tissue sampled. The diagnosis of focal SHML did not affect therapeutic decisions in these patients. Thus, the detection of focal SHML in these biopsy specimens was incidental and seems not to have had any clinical significance.

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