Sinus histiocytosis with massive lymphadenopathy (SHML), also known as Rosai-Dorfman disease, is a rare self-limiting disorder of histiocytes with unknown etiology. Sinus histiocytosis with massive lymphadenopathy is most common in children and young adults and is characterized by painless lymphadenopathy. Histologically there is a proliferation of sinus histiocytes with lymphophagocytosis or emperipolesis. On rare occasions, SHML has been associated with lymphoma, usually involving different anatomic sites and developing at different times. We report a case of concomitant SHML and nodal marginal zone lymphoma involving the same lymph node without involvement of other nodal or extranodal sites. The presence of concomitant SHML within the lymph node involved by nodal marginal zone lymphoma may represent the responsiveness of SHML histiocytes to B-cell–derived cytokines in lymphoproliferative disorders. To our knowledge, this is the first description of concomitant occurrence of SHML and nodal marginal zone lymphoma.

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Sinus histiocytosis with massive lymphadenopathy (SHML) was initially recognized by Destombes in 1965. In 1969, Rosai and Dorfman first described this disorder as a distinct clinicopathologic entity, characterized by painless cervical lymphadenopathy with a benign, self-limiting clinical course. Although peripheral lymphadenopathy is the most common mode of presentation, 30% to 40% of patients have extranodal manifestations. The most common extranodal sites are head and neck (sinuses, orbit, and ear), skin, and bone. Associated clinical and laboratory findings include fever, night sweats, weight loss, leukocytosis, elevated erythrocyte sedimentation rate, polyclonal hypergammaglobulinemia, and immune dysfunction. The diagnosis of SHML is readily established based on the presence of the histopathologic features including dilatation of sinuses due to proliferation of histiocytes with lymphophagocytosis or emperipolesis. Most affected individuals have a benign clinical course with spontaneous resolution, although rare fatal outcomes have been reported in patients with immunologic abnormalities. The etiology of SHML is unknown.

Sinus histiocytosis with massive lymphadenopathy is rarely associated with malignant neoplasms. There are only 20 reported cases of SHML identified in association with both non-Hodgkin lymphoma and Hodgkin lymphoma, usually involving different anatomic sites and developing at different times. To the best of our knowledge, this is the first case of simultaneous occurrence of SHML and nodal marginal zone lymphoma involving the same lymph node.

REPORT OF A CASE

An 80-year-old woman presented with a 2.0 cm subcutaneous mass in her right arm. The mass was painless and movable and had grown for several weeks. She reported no systemic symptoms including fever, weight loss, and night sweats. Physical examination revealed no evident organomegaly, lymphadenopathy, or other masses. Laboratory findings were within normal limits without absolute lymphocytosis or immunosuppressive abnormalities. Excision of the lesion was performed and the case was submitted in consultation to us.

Histologic examination revealed an architecturally effaced lymph node with a diffuse population of monotonous small- to intermediate-sized lymphocytes with mildly irregular nuclear outlines and inconspicuous nucleoli (Figures 1 and 2a). There were small numbers of admixed polyclonal plasma cells present without Dutcher bodies (Figure 2a). By immunohistochemistry, the atypical lymphocytes were positive for CD20 and CD79a, indicating a B-cell phenotype, with aberrant coexpression of CD43 and BCL2 (Figure 2, b through d). There was no coexpression of CD5, BCL6, and cyclin D1 in the B-cell population. CD3 revealed scattered background T lymphocytes. CD23 highlighted remnants of follicular dendritic meshworks, suggestive of colonized follicles. Immunoglobulin heavy chain gene rearrangement by polymerase chain reaction analysis was performed on formalin-fixed, paraffin-embedded tissue to reveal a clonal B-cell population. Chromosomal translocations associated with extranodal marginal zone lymphoma, t(11;18) and t(14;18) or trisomy 3, were not detected by fluorescence in situ hybridization. The combined morphologic, phenotypic, and molecular findings were diagnostic of a nodal marginal zone lymphoma.

In addition to the nodal marginal zone lymphoma, the nodal sinuses were markedly distended by a population of atypical histiocytes with enlarged vesicular nuclei and abundant to voluminous pale eosinophilic, focally vacuolated cytoplasm.
exhibiting engulfed lymphocytes (emperipolesis) (Figures 1 and 3). The histiocytes were positive for CD68 and S100 and negative for CD1a by immunohistochemical studies. S100 protein highlighted numerous histiocytes with emperipolesis (Figure 4). The morphologic and phenotypic findings were characteristic of SHML. The SHML was present in multiple areas throughout the lymph node and comprised approximately 40% of the lymph node. Epstein-Barr virus (EBV) was not detected in either the SHML or the nodal marginal zone lymphoma areas by EBV in situ hybridization. Parvovirus B19 capsid protein VP1 and VP2 immunohistochemistry was negative.

Further staging studies by fludeoxyglucose F 18 whole-body positron emission tomography scan with whole-body computed tomography scan revealed no abnormal metabolic activity except for borderline enlarged para-aortic lymph nodes and mild hepatomegaly. The patient has been followed carefully and did...
Painless lymphadenopathy is the most frequent clinical manifestation in SHML. Some patients experience antecedent nonspecific fevers, pharyngitis, and night sweats before lymph nodes become enlarged. The lymph nodes involved by SHML are hypermetabolic and positive on positron emission tomography. However, this classic clinical presentation is not required for diagnosis because isolated SHML has been well documented without nodal involvement. Because individuals with SHML present with a broad range of clinical presentations, a wide differential diagnosis is often elicited requiring careful histologic examination to avoid misinterpretation and prevent unnecessary treatment. Most patients with SHML have a benign clinical course with spontaneous resolution within 1 to 2 months. However, the prognosis tends to be worse in cases in which larger numbers of lymph nodes are involved as well as in cases involving extensive or critical sites.

The diagnosis of SHML is readily established based on the presence of characteristic histopathologic features. The lymph node architecture is altered by markedly expanded sinuses by static lymph and a mixed population of lymphocytes, plasma cells, and histiocytes. The sinus histiocytes exhibit enlarged vesicular nuclei with well-defined nuclear outlines, a single prominent nucleolus, and abundant pale eosinophilic, occasionally foamy cytoplasm containing variable numbers of intact lymphocytes. This engulfment of lymphocytes is referred to as lymphophagocytosis or emperipolesis. Mitoses are infrequent and necrosis is not typically observed. Immunohistochemical markers are important to distinguish SHML from other entities including Langerhans cell histiocytosis, malignant histiocytosis, hemophagocytic syndrome, nonspecific sinus hyperplasia, granulomatous lesions, Hodgkin lymphoma, melanoma, and carcinoma. The SHML histiocytes express monocyte/macrophage-associated antigens (CD68, HAM56, CD14, and CD64) and adhesion molecules (CD11b, CD11c, CD18, CD62L, and CD103). The SHML histiocytes are positive for S100 protein and negative for CD1a by immunohistochemistry.

Sinus histiocytosis with massive lymphadenopathy has remained a disorder of unknown etiology, and no characteristic cytogenetic or molecular abnormalities have been documented in the literature. Proposed mechanisms include a response to an occult infectious agent or a disorder of immune regulation, causing benign proliferation of sinus histiocytes. Serologic studies have revealed evidence of EBV infection in more than half of patients with SHML, but the results of in situ hybridization studies for latent or lytic EBV were negative in paraffin sections. It appears that EBV does not play a causative role in the pathogenesis of SHML. The presence of human herpesvirus 6 antigen in SHML tissues has been reported in the pathogenesis of SHML. In 1999, Middel et al suggested that stimulation of monocytes/macrophages via macrophage colony-stimulating factor represents the main mechanism for the pathogenesis of SHML.

In a small subset of patients with SHML, concurrent malignant neoplasms have been identified, including lymphomas, myelomas, melanoma, and carcinoma. Additionally, SHML has been described in association with both Hodgkin lymphoma and non-Hodgkin lymphoma and most commonly associated with follicular lymphoma and nodular lymphocyte predominant Hodgkin lymphoma.

In the setting of histiocytic reaction to lymphomas, lymphoma-associated hemophagocytic syndrome should be considered as an important differential diagnosis. Hemophagocytic syndrome (hemophagocytic lymphohistiocytosis) is a multisystem disorder with characteristic clinical and laboratory findings: fever; hepatosplenomegaly; cytopenias; hypertriglyceridemia and/or hyperlipidemia; hyperferritinemia; elevated soluble levels of interleukin 2 receptor; decreased or absent natural killer cell activity; and hemophagocytosis in bone marrow, cerebrospinal fluid, or lymph nodes. Lymphoma-associated hemophagocytic syndrome is an acquired, secondary hemophagocytic lymphohistiocytosis in association with lymphomas and has been reported mostly in adults. Unlike in SHML, EBV-infected T/natural killer cells appear to play a major role in the development of lymphoma-associated hemophagocytic syndrome as well as EBV-associated hemophagocytic lymphohistiocytosis without lymphoma.

In summary, this article describes the first case of simultaneous occurrence of nodal marginal zone lymphoma and SHML in the same lymph node. In our case, the patient was asymptomatic and the SHML was identified incidentally. This is similar to the reported cases of the same biopsy specimen involved by lymphoma and SHML. The concomitant SHML in this case is best considered as a nonspecific histiocytic response to the nodal marginal zone lymphoma.

References

Composite Rosai-Dorfman and Marginal Zone Lymphoma—Pang et al


