

Histiocytic Sarcoma : An Updated Literature Review Based on the 2008 WHO Classification

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Histiocytic sarcoma (HS) is an extremely rare malignant neoplasm showing morphologic and immunophenotypic evidence of histiocytic differentiation. The vast majority of previously reported HSs are now generally recognized to be misdiagnosed examples of non-Hodgkin lymphomas, predominantly diffuse large B-cell lymphoma or anaplastic large cell lymphoma. The recognition of such tumors parallels the development and widespread use of immunohistochemical techniques, along with the development of molecular genetic methods to detect *immunoglobulin (IG)* or *T-cell receptor (TCR)* gene rearrangement. The 2001 World Health Organization (WHO) definition of HS requires the absence of clonal B/T-cell receptor gene rearrangements. However, the 2008 WHO classification no longer strictly requires the absence of clonal *immunoglobulin heavy chain (IGH)* or *TCR* gene rearrangement for the diagnosis of HS. Recent studies demonstrated that HSs that occur subsequent to or concurrent with B- or T-lymphoblastic lymphoma/leukemia or mature B-cell neoplasms generally show clonal *IgH* and/or *TCR* gene rearrangement. These findings suggest the possibility of transdifferentiation of the two otherwise morphologically and immunohistochemically distinctive neoplasms. In addition, a recent study suggested clonal *IG* gene rearrangements may be detected at a high frequency in sporadic HS, indicating that a large subset of sporadic HSs may inherit the B-lymphocyte genotype. These findings provide new insights into the pathogenesis of HS, although the etiology of HS is still unknown. HS is a diagnosis of exclusion. It is necessary to rule out other diseases that could be misdiagnosed as HS with extensive immunophenotypical analysis before diagnosing HS. [*J Clin Exp Hematop* 53(1): 1-8, 2013]

Keywords: histiocytic sarcoma, immunophenotype, molecular genetics, WHO classification, differential diagnosis

INTRODUCTION

Histiocytic sarcoma (HS) is an exceedingly rare but aggressive hematopoietic tumor, showing morphologic and immunophenotypic features of mature tissue histiocytes. It is believed to be derived from monocytes/macrophages, which have major roles in the processing and presentation of antigens to T or B lymphocytes. Many inconsistencies in the terminology and diagnostic criteria of these lesions, including true histiocytic lymphoma, malignant histiocytosis, histiocytic medullary reticulosis, reticulum sarcoma and regressing atypical histiocytosis, have complicated their recognition and characterization. These tumors were initially considered histiocytic in origin on the basis of morphology alone. Subsequently, most of the neoplasms previously described as

histiocytic neoplasms have been shown to represent diffuse large B-cell lymphomas or peripheral T-cell lymphomas, most commonly anaplastic large cell lymphomas, by immunohistochemical techniques and only a small number have proven to be of true macrophage cell origin.

The 2001 World Health Organization (WHO) definition of HS required the absence of clonal B/T-cell receptor gene rearrangements.¹ However, the 2008 WHO classification no longer strictly requires the absence of clonal immunoglobulin heavy chain (*IgH*) or *T-cell receptor (TCR)* gene rearrangement for the diagnosis of HS and suggests that rare cases with antigen receptor gene rearrangement are most likely examples of transdifferentiation.² Recently, a high frequency of clonal *IGH/immunoglobulin κ chain (IGK)* rearrangement has been detected not only in HS with a history of or concurrent lymphoma/leukemia, but also in sporadic cases, providing new insights into the pathogenesis of HS.

The clinical features, immunophenotype, genetic findings, and diagnostic methods reported in the English literature since 1988 are summarized on the basis of the diagnostic criteria of the 2008 WHO classification.

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DEFINITION

HS is a malignant proliferation of cells showing morphological and immunophenotypic features of mature tissue histiocytes. Other diseases should be ruled out with extensive immunophenotypic workup before diagnosing HS.

EPIDEMIOLOGY

HS is extremely rare, accounting for less than 1% of all hematolymphoid neoplasms, although its true incidence remains to be determined owing to its rarity.^{3,4} Tumors can occur over a wide range of ages, from infant to elderly (6 months to 89 years ; median age, 46 years), showing a bimodal age distribution with a small peak at 0-29 years and a larger peak at 50-69 years (Fig. 1).³⁻⁴⁴ A male predominance is found (male : female = 82 : 56).³⁻⁴⁴

Some cases of HS occur subsequent to or concurrent with B- or T-lymphoblastic lymphoma/leukemia or mature B-cell neoplasms such as follicular lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, splenic marginal zone lymphoma and diffuse large B-cell lymphoma.^{11,12,21-35} Most associated mature B-cell lymphomas are low-grade B-cell lymphomas. The interval between the occurrence of lymphoma and that of HS is between 2 months and 17 years. It is noteworthy that there have been no cases of HS that precede the diagnosis of lymphoma. All cases associated with lymphoblastic lymphoma/leukemia are male, while cases associated with mature B-cell neoplasms show no sex predilection. The cases associated with lymphoblastic lymphoma/leukemia occur in children to young adults (4 years to 27 years ; median age, 13 years), corresponding to the aforementioned small peak in the age distribution of HS. In contrast, the cases that occur subsequent to or concurrent

with mature B-cell lymphomas develop in adults (42 years to 85 years ; median age, 61 years), corresponding to the large peak in the age distribution.

A subset of cases is associated with primary mediastinal germ cell tumors, especially in young male adults.^{18,20}

CLINICAL FEATURES

Lymph nodes are the most common site of presentation, although a variety of extranodal sites may be affected, particularly the gastrointestinal tract, spleen, soft tissue and skin (Fig. 2). Other sites of involvement include head and neck regions, salivary gland, lung, mediastinum, breast, liver, pancreas, kidney, uterus, central nervous system, bone and bone marrow. Cases can be localized or disseminated.

Systemic symptoms such as fever, fatigue, night sweats, weight loss and weakness are relatively common. Lymphadenopathy is also often seen. Skin manifestations (ranging from a benign-appearing rash to solitary lesions to innumerable tumors on the trunk and extremities), intestinal obstruction, hepatosplenomegaly with associated pancytopenia and lytic bone lesions may occur.² HSs of the spleen were often associated with splenomegaly with severe hypoalbuminemia and thrombocytopenia.^{12,17-19,26,41}

MORPHOLOGY

The tumor comprises a diffuse non-cohesive proliferation of large cells, but a sinusoidal or paracortical distribution may be seen in lymph node, liver and spleen. The individual neoplastic cells are usually large and round to oval in shape (Fig. 3). However, focal areas of spindle features may be present. The cytoplasm is usually abundant and eosinophilic, often foamy, vacuolated or clear (Fig. 4). Hemophagocytosis may occur in the neoplastic cells. The nuclei are generally

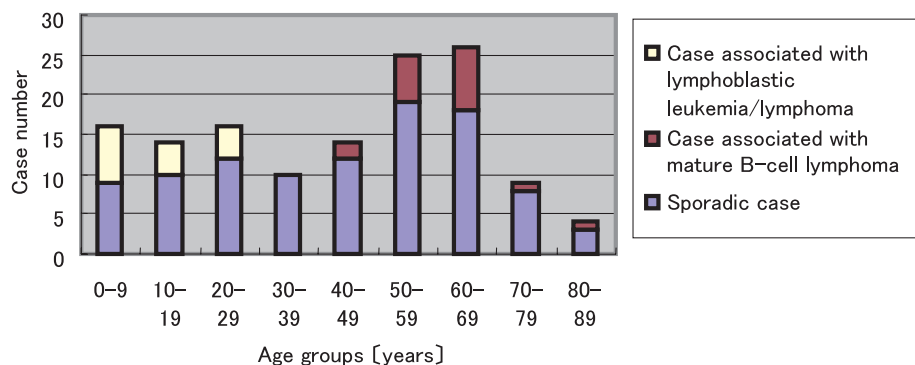


Fig. 1. Histiocytic sarcoma occurs over a wide range of ages, showing a bimodal age distribution with a small peak at 0-29 years and a larger peak at 50-69 years. The cases associated with lymphoblastic lymphoma/leukemia occur in children to young adults, corresponding to the small peak in the age distribution, whereas the cases that occur subsequent to or concurrent with mature B-cell lymphomas develop in adults, corresponding to the large peak in the age distribution.

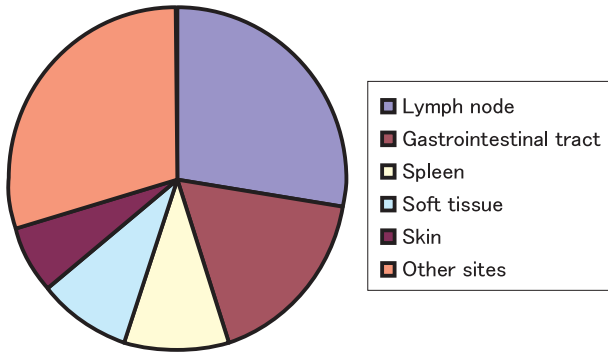


Fig. 2. The lymph node is the most common site, followed by the gastrointestinal tract, spleen, soft tissue and skin.

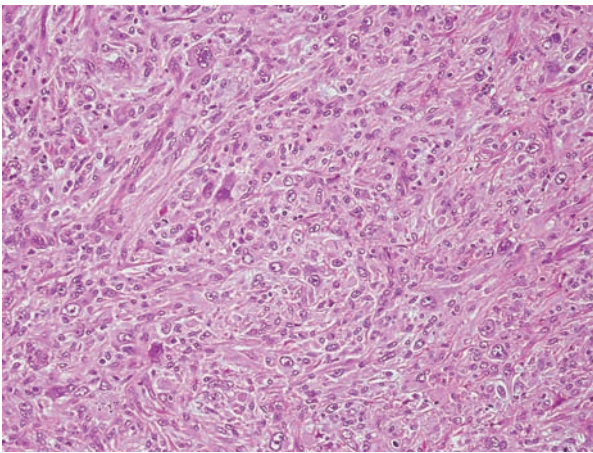


Fig. 3. The tumor comprises a diffuse non-cohesive proliferation of large cells. The neoplastic cells are round to oval in shape, but focal areas of spindle features are observed.

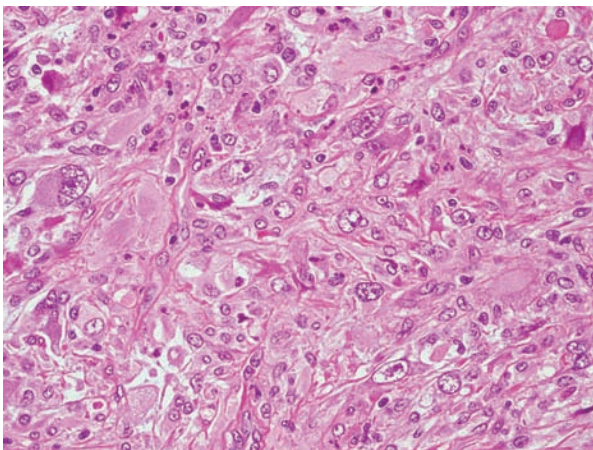


Fig. 4. The cytoplasm of the tumor cells is abundant and eosinophilic. The nuclei are large, round to oval, and often eccentrically placed with vesicular chromatin and nucleoli ranging from indistinct to large.

large, round to oval, grooved, indented, convoluted or irregularly folded, and often eccentrically placed (Fig. 4). Nuclear atypia varies from mild to severe. Multilobated, binucleated or large multinucleated forms are commonly seen. Occasional bizarre cells with pleomorphic hyperchromatic nuclei and coarse chromatin are identified. The chromatin pattern is usually vesicular, with nucleoli ranging from indistinct to large. Mitotic activity is a consistent finding, but varies in degree from case to case. Necrosis may be present. A variable number of reactive cells including small lymphocytes, plasma cells, benign histiocytes, neutrophils and eosinophils may be seen.

IMMUNOPHENOTYPE

By definition, there is the expression of one or more histiocytic markers, including CD163, CD68 (KP1 and PG-M1) and lysozyme, with typical absence of B-cell- and T-cell-related markers, and Langerhans cell (CD1a, langerin/CD207), follicular dendritic cell (CD21, CD23, CD35, CAN. 42), epithelial (pancytokeratin, EMA), melanocytic (HMB-45, Melan A) and myeloid cell (CD13, CD33, myeloperoxidase) markers. Tumor cells can express a variety of histiocytic markers such as CD4, CD11c, CD14, CD15, CD43, CD45, CD45RO, MAC387 and HLA-DR. The Ki-67 index is variable. Tumor cells are negative for CD30. Some cases can be S-100 protein-positive, but staining is often weak and patchy rather than uniform. A subset of cases is positive for CD1a, although the staining is usually limited and focal.⁹ The tumors were, usually, at least focally positive for CD31, in line with a report demonstrating that CD31 often stains macrophages.^{9,45} It should be emphasized that none of the antibodies is specific for histiocytic differentiation. Therefore, evaluation with a panel of antibodies in the context of the morphology is important.

CD68 (KP1 and PG-M1) is an available marker most frequently used to highlight the macrophage/histiocytic deviation of tumors with good reproducibility, showing granular cytoplasmic staining (Fig. 5). This CD68 antigen is localized to lysosomes, phagosomes and neutrophil primary granules, generally being regarded as organelle- rather than cell-lineage-specific. Therefore, it is not considered an exclusive marker of cells of macrophage/histiocytic derivation. In addition to cells in the monocyte/macrophage lineage, CD68 reacts with other neoplasms in the differential diagnosis of HS, such as melanoma, carcinoma, some lymphomas and dendritic cell tumors. Compared with KP1, PG-M1 has demonstrated greater restrictivity.

CD163, a hemoglobin scavenger receptor, is a new immunohistochemical marker of monocytes and histiocytes, showing membranous/cytoplasmic staining (Fig. 6). Its expression is primarily limited to neoplasms of macrophage/histiocytic derivation, as well as non-neoplastic monocytes, and is more

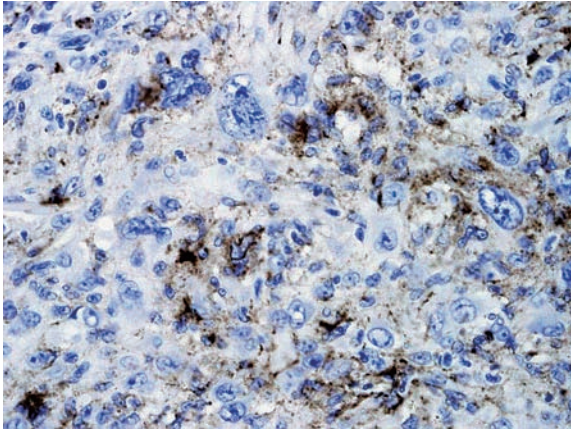


Fig. 5. The tumor cells are positive for CD68, showing granular cytoplasmic staining.

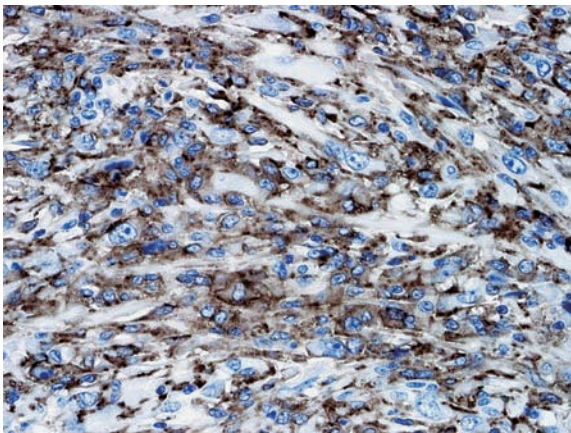


Fig. 6. CD163 immunohistochemistry highlights membranous/cytoplasmic reactivity in the neoplastic cells.

specific than other macrophage/histiocytic markers such as CD68.^{46,47} Therefore, CD163 may have significant diagnostic utility in separating specific tumors with macrophage/histiocytic deviation from other entities in their differential diagnosis.

Cases that occur subsequent to or concurrent with mature B-cell lymphoma (especially follicular lymphoma) may retain the primary tumor's immunophenotypic features to a certain extent, such as BCL6 nuclear positivity and expression of BCL2 protein, while showing the morphologic and immunophenotypic profiles diagnostic of HS.^{30,33,35} In addition, some cases showed nuclear positivity of OCT-2, a B-cell-associated transcription factor. Of interest, Chen *et al.* recently reported that 4 of 7 sporadic HS cases with detectable clonal *IGH* gene rearrangement expressed OCT-2.¹³

Association of viral infection such as Epstein-Barr virus has not been detected.

GENETIC AND MOLECULAR FINDINGS

The 2001 WHO definition of HS requires the absence of clonal *IGH* or *TCR* gene rearrangements.¹ Nonetheless, rare cases of HS with detectable *IG* gene rearrangements have been described.¹⁰ In 2008, Feldman *et al.* provided compelling evidence that patients with follicular lymphoma and associated concurrent/subsequent HS share identical genotypic features, suggesting the possibility of transdifferentiation or dedifferentiation of the two otherwise morphologically and immunohistochemically distinctive neoplasms.³⁵ On the basis of these observations, the 2008 WHO classification no longer strictly requires the absence of clonal *IGH* or *TCR* gene rearrangement for the diagnosis of HS and suggests that rare cases with antigen receptor gene rearrangement are most likely examples of transdifferentiation.²

Interestingly, all examined HS cases that occur subsequent to or concurrent with B- or T-lymphoblastic leukemia/lymphoma or mature B-cell lymphoma, most of which are low-grade B-cell lymphomas, revealed clonal B/T-cell receptor gene rearrangement. The HS generally shares the clonal markers of the previous leukemia/lymphoma, such as *IGH* gene rearrangement, *IGK* gene rearrangement, *TCR* γ chain gene rearrangement, *IGH/BCL2* fusion gene (i.e. a genetic hallmark of follicular lymphoma), and *CCND1-IGH* rearrangement, suggesting the possibility of transdifferentiation or dedifferentiation of two distinctive neoplasms.^{12,21,23,24,26,27,29-35}

How neoplastic B cells convert to histiocytic cells is still unknown. However, two major hypotheses have been proposed for the molecular transformation of B-cell lymphoma to HS. One is the direct transdifferentiation of neoplastic B cells into malignant histiocytes. The other involves a two-step process of transformation with first dedifferentiation of neoplastic B cells to early progenitors and subsequent redifferentiation along the histiocytic lineage. In addition, a third theoretical possibility would be the presence of a common neoplastic progenitor with differentiation along both B-cell and histiocytic/dendritic lineages.

It has been postulated that changes in transcription factor expression and/or activity may have led to transdifferentiation from a lymphoid phenotype to a histiocyte phenotype.³⁵ Of particular interest are studies showing that *PAX5* expression is critical to maintaining the B-cell phenotype with deletion of *PAX5* causing mature B cells to dedifferentiate to either macrophages or uncommitted precursors.^{48,49} It has also been demonstrated that B cells convert to macrophages by inhibition of *PAX5* expression in conjunction with forced expression of *C/EBP* α and β .⁴⁸ In fact, all examined HS were negative for *PAX5*, despite genotypic evidence of a B-cell derivation.

These genetic findings are also observed in some sporadic cases. Chen *et al.* reported that six of 14 sporadic cases examined (43%) showed clonal *IGH* (\pm *IGK*) gene rearrange-

ments, whereas one case (7%) showed only clonal *IGK* gene rearrangement.¹³ Among cases with clonal *IGH* and/or *IGK* gene rearrangements, one case showed t(14;18) by PCR and FISH.¹³ Of interest, all 7 *IGH*- and/or *IGK*-positive cases were negative for PAX5 and BOB. 1, whereas 4 of 7 cases were positive for OCT-2.¹³

DIFFERENTIAL DIAGNOSIS

Diagnosis of HS requires recognition of the atypical histiocytic morphology of tumor cells and expression of histiocyte-associated markers, followed by exclusion of the many differential diagnoses using an extensive immunohistochemical panel. The differential diagnosis includes reactive histiocytic proliferations, dendritic cell neoplasm, large cell non-Hodgkin lymphoma, especially anaplastic large cell lymphoma and diffuse large cell lymphoma, malignant melanoma, undifferentiated large cell carcinoma and monocytic leukemia.

Reactive histiocytic proliferations and HS share the expression of histiocyte-associated markers. Therefore, the distinction between these two diseases rests on cytologic features. HS features cells with cytologically malignant nuclei distinct from the bland nuclei and distinctive round nuclei with a fine chromatin pattern found in most reactive histiocytic proliferations.

Dendritic cell sarcomas, particularly interdigitating dendritic cell sarcoma, may also be morphologically confused with HS. In addition, both neoplasms may have S-100 protein- and CD68-positive cells. Features favoring interdigitating dendritic cell sarcoma include long dendritic cell processes, convoluted nuclei, more diffuse and stronger staining for S-100 protein and variable and often weaker staining for CD68. Typical morphology of Langerhans cell histiocytosis, i.e., grooved, indented, folded, or lobulated nuclei with fine chromatin and thin nuclear membrane, a conspicuous infiltration of eosinophils, immunohistochemical detection of CD1a and langerin/CD207, and the ultrastructural presence of Birbeck granules, supports the diagnosis of Langerhans cell histiocytosis and rules out HS. The neoplastic cells of Langerhans cell sarcoma display overtly malignant cytology, but retain characteristic features of Langerhans cells such as nuclear features and the immunophenotypical profile. The presence of features of follicular dendritic cells such as spindle to ovoid cell proliferation forming fascicles, storiform patterns and whorls, and the expression of follicular dendritic cell markers including CD21, CD23, and CD35 favors follicular dendritic cell sarcoma. The International Lymphoma Study Group has highlighted the use of a panel of several immunophenotypic markers (e.g., CD68, CD1a, S-100, CD2, CD35) as necessary for correct identification of cases of true HS and dendritic cell sarcomas.⁸ In addition to the aforementioned immunohistochemical panel, the use of CD163 seems

to be helpful in diagnosis.

Malignant melanoma and HS could be morphologically similar. Additionally, both tumors may show S-100 protein and CD68 expression. However, HS lacks more specific melanoma markers such as HMB-45 and Melan-A, while malignant melanoma lacks the expression of the specific histiocytic marker CD163. The presence of melanin pigment in the cytoplasm of tumor cells and the aggregation of melanophages is helpful in the diagnosis of malignant melanoma.

Carcinoma, especially undifferentiated carcinoma, occasionally exhibits abundant eosinophilic cytoplasm, closely resembling HS. Negative staining for pan-cytokeratin and epithelial membrane antigen may not necessarily rule out carcinoma. Moreover, a subset of carcinomas are positive for CD68 (both KP1 and PG-M1).^{46,47} Adequate tissue sampling to detect epithelial origin and more obviously differentiated areas could be helpful to distinguish carcinoma from HS. The expression of CD163 is helpful to exclude carcinoma.

Anaplastic large cell lymphoma is the non-Hodgkin lymphoma most frequently confused with HS, given its propensity for involvement of the sinusoids and its frequent cytologic pleomorphism. In fact, many cases previously regarded as malignant histiocytosis have been found actually to represent anaplastic large cell lymphoma. A constellation of findings, such as the expression of CD30, ALK-1 and cytotoxic markers, the demonstration of T-cell antigens (excluding the nonlineage-specific CD4 and CD43), the presence of the characteristic cytogenetic abnormality t(2;5) and the demonstration of clonal *TCR* gene rearrangements, generally differentiates anaplastic large cell lymphoma from HS. Diffuse large B-cell lymphoma is another lymphoma that needs to be differentiated from HS. The expression of B-cell markers (excluding OCT-2) may be used to distinguish diffuse large B-cell lymphoma from HS, although the presence of clonal *IGH/IGK* gene rearrangement does not rule out HS. Both T- and B-cell lymphomas may have large numbers of reactive histiocytes (e.g., Lennert lymphoma and T-cell/histiocytic-rich B-cell lymphoma); therefore, it is important to evaluate staining on the cytologically atypical cells.

Although monocytic leukemia is usually systemic at presentation, it rarely presents as an extramedullary mass without blood and marrow involvement. There is the remote possibility that it may be histologically confused with HS. However, monocytic leukemia expresses myeloid markers, such as myeloperoxidase, CD33 and CD34, whereas HS does not. Additionally, monocytic sarcoma can be recognized by the much smaller cell size and more monotonous appearance of the tumor cells.

CLINICAL COURSE

HS most often presents at an advanced clinical stage, with limited response to chemotherapy and a high mortality. HS is

an aggressive neoplasm, and most patients die of progressive disease within 2 years. Nonetheless, some patients may respond to chemotherapy with/without radiotherapy and have a relatively indolent clinical course.⁹ Additionally, a subset of cases presenting with localized disease have a favorable long-term outcome.^{9,10} Stage at presentation and tumor size seem to impact on prognosis. However, there is no consensus on the prognostic factors and the standard treatment approach due to the rarity of the disease, although lymphoma-based protocols are often used.

CONCLUSION

In summary, HS is a malignant proliferation of cells showing morphological and immunophenotypic features of mature tissue histiocytes. It occurs over a wide range of ages and shows a male predominance. Some cases of HS are associated with B- or T-lymphoblastic lymphoma/leukemia or mature B-cell neoplasms, most of which are low-grade B-cell lymphomas. The cases associated with lymphoblastic lymphoma/leukemia occur in children to young adults, whereas the cases that occur subsequent to or concurrent with mature B-cell lymphomas develop in adults. Lymph nodes are the most common site of presentation, although a variety of extranodal sites such as the gastrointestinal tract, spleen, soft tissue and skin may be affected. Histologically, the tumor shows diffuse infiltration of large, round to ovoid pleomorphic cells. By definition, there is the expression of one or more histiocytic markers, including CD163, CD68 and lysozyme, with typical absence of B-cell- and T-cell-related markers, and dendritic cell, epithelioid and myeloid cell markers. CD163, a new immunohistochemical marker of monocytes and histiocytes, is more specific than other macrophage/histiocytic markers such as CD68 and may have significant diagnostic utility. HS most often presents at an advanced clinical stage, with limited response to chemotherapy and a high mortality. No standard treatment has been established for HS. Most patients die from disseminated disease within two years, although there are some survivors. HS is a diagnosis of exclusion. The diagnosis is based on histological and immunohistochemical evidence of histiocytic differentiation supported by an extensive immunophenotypic analysis that excludes other large cell malignancies in the differential diagnosis.

The etiology of HS is unknown. However, recent studies demonstrated that HSs associated with lymphoma/leukemia generally show clonal *IG ± TCR* gene rearrangement. In addition, clonal *IGH (± IGK)* gene rearrangements may be detected at a high frequency in sporadic HS, suggesting that a large subset of sporadic HSs have inherited B-lymphocyte genotypes. These data provide additional evidence to support the view of a close association between “B-cell lymphoma” genotype and HS. The exact mechanism governing the con-

version of lymphoblastic lymphoma/leukemia or mature B-cell lymphoma to HS remains to be elucidated.

Recent biological developments indicated the existence of two major subtypes of M1 and M2 macrophages. However, the relationship of this phenotype delineation with the biological behaviors and pathogenesis of HSs remains to be clarified.

Continued investigation is necessary to obtain a full understanding of the clinicopathological and genotypic features of this rare tumor and to elucidate further the pathogenesis of this neoplasm.

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