Original Study

Clinicopathologic Features and Clinical Outcome Differences in De Novo Versus Secondary Histiocytic Sarcomas: A Multi-institutional Experience and Review of the Literature

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Abstract

Histiocytic sarcoma (HS) is a rare neoplasm that generally behaves aggressively; however, an in-depth study of the clinicopathologic features has not been performed. We explored 23 unique cases of HS occurring as de novo or secondary malignancies. Patients with a secondary HS had lower mean survival by 58.2 months (P = .001). This suggests secondary HSs behave more aggressively than de novo HSs.

Introduction: Histiocytic sarcoma (HS) is a rare malignant neoplasm that can occur in patients with a history of treatment for hematologic or solid tumors. Because no optimal treatment has been defined and standardized, the treatment modalities used and outcomes reported have been highly variable. In the present study, 3 major institutions explored the clinicopathologic features of de novo and secondary HS. **Materials and Methods:** After institutional review board approval, clinical, histopathologic, and immunophenotypic data were collected from patients with a diagnosis of HS and treated at the University of Alabama at Birmingham, University of New Mexico, or Brooke Army Medical Center from January 1, 2003 to December 31, 2016. **Results:** The databases revealed 23 unique cases of HS. The mean age was 55.4 years (range, 5-84 years) and the male-to-female ratio was 0.92. The mean follow-up period was 89.82 months (range, 14-172 months). Of the 23 patients with HS, 6 had a history of an unrelated malignancy treated with chemotherapy or radiotherapy, with a mean delay of 42.2 months (range, 12-91 months). The mean overall survival during the study period was 54.1 months. The overall survival of those with de novo HS was 70 months compared with 11.8 months for those with secondary HS, with a mean difference of 58.2 months (95% confidence interval, 26.2-90.2 months; P = .001). **Conclusion:** The shorter overall survival with secondary HS suggests a more aggressive course than that with de novo disease. Larger scale studies are needed to further investigate the biology and genetics of HS.

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Introduction

Histiocytic sarcoma (HS) is an extraordinarily rare neoplasm with very few case reports and case series reported.[1] Although most cases developed in adults with a mean age of 52 years, all ages can be affected, with a slight male predilection.[2,3] Currently, the tumor has an unknown etiology and often presents at extranodal sites, in particular, in the gastrointestinal tract, skin, or soft tissue.[3] Rarely, a more systemic presentation with multiple sites of involvement can be seen. Some cases have been reported to be associated with mediastinal germ cell tumors or with another hematologic malignancy such as lymphoma, myelodysplasia, or leukemia and can present before, concurrently, or after the diagnosis of HS.[1,4]

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The diagnosis of HS can be challenging owing to the unclear distinction between neoplastic and non-neoplastic proliferation of histiocytes, such as reactive histiocytosis, and requires a thorough clinical, morphologic, and immunohistochemical examination. HS often presents as a diffuse process in viscera and skin and as a sinusoidal pattern in the lymph nodes. The cytology of the tumor cells varies from round to oval to spindle-shaped in appearance, with discohesive sheets of large cells. Cells can have foamy cytoplasm, and occasional hemophagocytosis can be seen. It is common for the malignant cells to have cytologic atypia with prominent nuclear irregularities; however, a bland appearance can also be seen. The cells can appear similar to other high-grade large cell neoplasms such as melanoma, poorly differentiated carcinoma, and large cell lymphoma. On immunohistochemical staining, the cells will be positive for ≥ 1 histiocytic lineage markers, including CD163, CD68, and lysozyme.[4] CD45, CD45RO, and HLA-DR also are often positive.[1] HS is typically negative for Langerhans cells and other dendritic cell markers, including CD1a, langerin, CD21, and CD35. HS will also be negative for myeloid markers such as CD33, CD13, and myeloperoxidase; occasionally, CD15 expression will be seen. S-100 protein can be focally positive but usually demonstrates weak expression.[1,4]

Little is known about the molecular mutations associated with HS. However, clonal immunoglobulin gene rearrangements can be seen, especially in cases associated with lymphoid malignancies. In those associated with a germ cell tumor, identical genetic changes will typically be seen in both malignancies.[5] BRAF V600E mutations have been found in some cases.[6] Although current molecular findings have suggested > 1 mutation might be responsible for an otherwise morphologically similar tumor, the direct etiology remains unknown.[7]

Clinically, HS is an aggressive neoplasm with a poor response to therapy, and the vast majority of patients die after disease progression. To date, no optimal treatment regimen is available for HS, and only a few case reports and case series have discussed the treatment regimens prescribed, which had varying degrees of success.[3,8-12] Outcomes from a case series suggested that localized versus metastatic disease at the diagnosis did not change the severity of disease, and neither adjuvant nor neoadjuvant therapy improved overall survival, even compared with observation.[13] In addition, it is unlikely that most of the unsuccessful treatments would have been pursued for publication.

At present, little has been established for HS regarding predictive factors. Although the overall survival is known to be low, no data have been reported regarding survival in different populations. In particular, a distinction between primary and secondary HS has not been made. On rare occasions, HS can arise in patients previously treated for other malignancies and has been defined as secondary HS.[14] In the present study, we explored the novel idea that secondary HS behaves differently clinically from de novo disease.

Materials and Methods

Patient Identification and Data Collection

Three major academic centers retrospectively identified cases of HS diagnosed according to the World Health Organization guidelines from January 1, 2003 to December 31, 2016. Cases were included if the original diagnosis was made at the academic center and the original slides were available for review. Cases were excluded if hematoxylin and eosin–stained and immunohistochemical (IHC)-stained sections were unavailable. Patient identification and slide location began after approval from each academic center's institutional review board. The IHC stains used for the initial pathologic diagnosis of HS included CD45, CD68, CD163, CD14, CD1a, CD21, and S100. Next generation sequencing was available for 1 of the patients with secondary HS.

Table 1 Study Demographic Information

Demographic Data	Value
Age, y	
Mean	55.4
Range	5-84
Male-to-female ratio	0.92
Histiocytic sarcoma, n	
Primary	17
Secondary	6

The patient data, including demographic data, history of previous malignancy, location of the HS at presentation, and treatment rendered, were collected from the appropriate electronic medical records. The patients identified during the study period had their survival status determined by November 1, 2017. The range and mean follow-up time were recorded. The hematoxylin and eosin and IHC sections were reviewed to confirm the diagnosis, and the IHC staining results were recorded in a standardized document. The patient data were de-identified and transferred to 1 of us (D.R.B.) for compilation and statistical analysis.

Statistical Analysis

The Kaplan-Meier method was used to determine the difference between primary and secondary HS survival. Appropriate 95% confidence intervals (CIs) were determined. The remaining statistical data were generated with support from Excel software.

Results

A total of 23 unique cases with appropriate clinical information and pathologic materials available were identified. The mean age at

Table 2 Distribution of Histiocytic Sarcomas

Location	n (%)
Head and neck	6 (26)
Lower extremity	5 (22)
Lung	3 (13)
Upper extremity	2 (9)
Liver	1 (4)
Breast	1 (4)
PEG tube site	1 (4)
Bone marrow	1 (4)
Mediastinum	1 (4)
Pancreas	1 (4)
Brain	1 (4)

Abbreviation: PEG = percutaneous endoscopic gastrostomy.