Histiocytic Sarcoma

Review, Discussion of Transformation From B-Cell Lymphoma, and Differential Diagnosis

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Context.—Histiocytic sarcoma is a rare neoplasm of mature histiocytes with an aggressive clinical course that can arise de novo or from a low-grade B-cell lymphoma. In particular, chronic lymphocytic leukemia/small lymphocytic lymphoma is a very common malignancy in the Western hemisphere, and most cases of chronic lymphocytic leukemia/small lymphocytic lymphoma have an indolent course and behavior. However, 2% to 8% of chronic lymphocytic leukemia/small lymphocytic lymphoma cases transform. Histiocytic sarcomatous transformation is rare and portends poor prognosis.

Objective.—To review the clinical features, morphology, and key points related to the differential diagnosis for histiocytic sarcoma. We discuss recent understanding of the biology underlying transformation.

Data Sources.—University of Michigan case and review of pertinent literature about histiocytic sarcoma and morphologic differential diagnosis.

Conclusions.—Histiocytic sarcoma is a rare histiocytic neoplasm that can arise as a result of transdifferentiation from low-grade B-cell lymphomas, and has a wide differential diagnosis including other histiocytic/dendritic cell neoplasms, myeloid neoplasms, lymphomas, melanoma, and carcinoma. However, some key morphologic and immunohistochemical features allow for accurate classification.

Histiocytic sarcoma is a rare neoplasm of mature histiocytes, and is considered to be a true hematopoietic tumor. It can present as a primary malignancy or, less commonly, a secondary malignancy. There are multiple reports of presumed transdifferentiation from low-grade B-cell lymphoma to histiocytic sarcoma; this accounts for approximately one-fourth of cases. Reported primary lymphomas include chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma, and extranodal marginal zone lymphoma. Histiocytic sarcoma has also been reported as a second malignancy after chemotherapy for germ cell tumors of the gonads or mediastinum. Histiocytic proliferations associated with acute monoblastic leukemia are excluded from this diagnosis.

Epidemiology and Clinical Features

Histiocytic sarcoma commonly presents as a painless solitary mass at an extranodal site (gastrointestinal tract, soft tissue, skin, spleen, or liver). Many patients have systemic (B) symptoms such as fever, night sweats, or weight loss. Based on the cases reported in the literature, the median age at diagnosis is 51 years (range, 1–89 years), with a slight male predominance.

Morphology

Histiocytic sarcoma usually shows a diffuse architecture involving either nodal or extranodal tissue. A sinusoidal or paracortical pattern can be seen in lymph node, liver, or spleen. The neoplastic cells are large (usually >20 μm) and are round to oval with abundant eosinophilic cytoplasm and well-defined cell borders. The neoplastic nuclei are round to oval or folded, with fine to vesicular chromatin, variably prominent nucleoli, and notable pleomorphism. Cytoplasmic vacuoles or xanthomatous appearance can be noted in some cases. Neoplastic giant cells or spindle cells can be seen. Mitotic activity may be frequent, and necrosis is common. Admixed Langerhans cells can be present, as long as they are a minor component. Although the neoplastic cells are usually discohesive, they may rarely appear as epithelioid clusters and sheets. When soft tissue is involved, the tumor shows infiltrative borders. Hemophagocytosis or emperipolesis by neoplastic cells can be present. There is usually a prominent inflammatory background consisting of neutrophils and lymphocytes.

Immunohistochemistry

At least one histiocytic or histiocytic-associated marker (CD163, CD68, CD11c, lysozyme) will be positive in cases of histiocytic sarcoma.
histiocytic sarcoma. CD163 should show a membranous and cytoplasmic pattern; expression is primarily limited to macrophages/histiocytes as well as nonneoplastic monocyt es.\textsuperscript{14} CD68 is considered positive when diffuse granular cytoplasmic staining is present, but is not specific to histiocytes. Lysozyme should show a cytoplasmic and/or Golgi/paranuclear pattern of staining. Human leukocyte antigen–antigen D related (HLA-DR) and CD45 are often positive. S100 is often positive, but only in a minor subset of cells. A subset of cases is positive for CD1a, but this is limited and focal.\textsuperscript{2} Rare cases can show weak staining for CD15 or CD30.\textsuperscript{5} Follicular dendritic cell markers, CD13, CD33, and myeloperoxidase are negative.

In secondary histiocytic sarcoma arising from B-cell lymphomas, there may be retention of some B-cell markers, including weak paired box protein 5 (PAX5) expression.\textsuperscript{4,6,14,16} The Ki-67 proliferative index is generally between 5% and 50%.

**MOLECULAR FINDINGS**

There are no distinctive molecular findings specific for histiocytic sarcoma. However, histiocytic sarcoma cases with preceding B-cell lymphoma and exhibiting transdifferentiation can share molecular aberrations with the B-cell lymphoma. An example of CLL/SLL with transformation to histiocytic sarcoma and del(13q) in both components is shown in Figure 1, A and B. Chromosome 17p abnormalities may increase the risk of transdifferentiation to histiocytic or dendritic cell sarcoma.\textsuperscript{17} BRAF V600E mutations have also been described, though infrequently, in histiocytic sarcoma.\textsuperscript{18}

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**Figure 1.** Transdifferentiation of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Fluorescence in situ hybridization confirms homozygous deletion of 13q14 in CLL/SLL (A) and histiocytic sarcoma (B) (original magnification X400).
DIFFERENTIAL DIAGNOSIS

Classic Hodgkin Lymphoma

Classic Hodgkin lymphoma (CHL), like histiocytic sarcoma, can arise in a background of CLL/SLL. Both CHL and histiocytic sarcoma may have a prominent inflammatory background (Figure 2, A), and histiocytic sarcoma sometimes shows a nodular pattern with sclerosis reminiscent of CHL. Cells with true Reed-Sternberg or Hodgkin morphology favor the diagnosis of CHL (Figure 2, B). The syncytial variant in particular bears resemblance to histiocytic sarcoma because of the presence of cohesive clusters or sheets of Reed-Sternberg cell variants. Additionally, the clinical presentation is aggressive, with many patients presenting at high stage or with life-threatening airway obstruction. Immunohistochemical evaluation can easily distinguish these entities. The large neoplastic cells in CHL are positive for CD15 and CD30 with weakly positive PAX5, and negative for CD45 and histiocyte markers.

Rosai-Dorfman Disease

Rosai-Dorfman disease bears at least superficial resemblance to histiocytic sarcoma because of the presence of large histiocytes with abundant cytoplasm and emperipolesis. However, by contrast, its vesicular nuclei lack cytologic atypia. In many cases of histiocytic sarcoma, the cell-in-cell appearance is due to phagocytosis (Figure 2, C) rather than true emperipolesis; that is, cells present in the cytoplasm are phagocytosed and cellular debris can be identified. In true emperipolesis, the emperipoletic cells are alive within the cytoplasm. Nodal involvement by Rosai-Dorfman disease shows large histiocytes with abundant cytoplasm and central nuclei in a prominent sinusoidal pattern (Figure 2, D). There is greater diagnostic difficulty at extranodal sites because of the decreased frequency of emperipolesis and the sometimes spindly nature of the histiocytes in a fibrotic background. Rosai-Dorfman disease typically has abundant plasma cells in the background. The large histiocytes are positive for S100 (variable percentage of cells) and negative for CD1a, CD207/lysozyme is positive, it is often in only a subset of cells. In contrast to histiocytic sarcoma, it tends to present with rapid growth. Proposed etiologic factors include immunosuppression, viruses, and prior hematologic diseases including Langerhans cell histiocytosis, lymphoma, or leukemia. As in histiocytic sarcoma, the most commonly involved sites include skin and soft tissue. When LCS is present in lymph nodes, the pattern may be diffuse, nodular, or sinusoidal. There may only be a small subset of cells resembling normal Langerhans cells, with longitudinally grooved and folded nuclei and abundant cytoplasm. The complexity of nuclear contours is greater in LCS (Figure 2, G) than in histiocytic sarcoma (Figure 2, H). Small foci of eosinophils are commonly seen in the background. Langerhans cell sarcoma is positive for CD1a, S100, and CD207/lysozyme, and negative for CD21, CD35, and CD68. When lysozyme is positive, it is often in only a subset of cells. In contrast to normal Langerhans cells, LCS is positive for CD56 and CD31. HLA-DR shows paranuclear dotlike expression in LCS, and can help distinguish neoplastic Langerhans cells from reactive Langerhans cells.

Myeloid Sarcoma

Myeloid sarcoma is a neoplasm that is usually associated with acute myeloid leukemia, myeloproliferative neoplasm, or myelodysplastic syndrome. Myeloid sarcoma can occur de novo or concurrently with or after diagnosis of a myeloid neoplasm. There is a slight male predominance, and the average patient is middle-aged. Common sites include lymph nodes, gastrointestinal tract, skin, and soft tissue. Approximately 40% of myeloid sarcomas are predominantly composed of monocytic or myelomonocytic cells, and half of monoblastic myeloid sarcomas occur in the skin. A small subset of cases show well-differentiated histiocytic cytology.

In nodal sites, sinusoidal or paracortical involvement is seen. Extranodal myeloid sarcoma shows diffuse or single-file growth. Importantly, myeloid sarcoma is less pleomorphic than histiocytic sarcoma (compared in Figure 2, E and F). Although CD68 is commonly expressed in myeloid sarcoma, markers such as myeloperoxidase, CD13, or CD33 can aid in accurate diagnosis. Ki-67 proliferative index is usually lower than 50%.

Langerhans Cell Sarcoma

Langerhans cell sarcoma (LCS) is a rare neoplasm of Langerhans cells that usually arises de novo, although it can progress from either Langerhans cell histiocytosis or a low-grade B-cell lymphoma. Langerhans cell sarcoma is an aggressive disease with a mortality rate of 50% and death often within 2 years. Surgical excision appears to be the best treatment option, with or without chemotherapy.

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Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma is included in the differential diagnosis of histiocytic sarcoma, as it is another large cell neoplasm that may arise as high-grade transformation of a low-grade B-cell lymphoma. Approximately 2% to 8% of patients with CLL/SLL transform to a more aggressive B-cell lymphoma, usually diffuse large B-cell lymphoma (Richter syndrome). The annual incidence rate is 0.5% for all CLL or 1% for treated CLL. The median overall survival in Richter syndrome is 2.1 years. Photomicrographs demonstrating large cell transformation of CLL/SLL are shown in Figure 3, A and B (histiocytic sarcoma and diffuse large B-cell lymphoma, respectively). Immunohistochemistry is useful, as diffuse large B-cell lymphoma will express B-cell markers (CD19, CD20, CD22, CD79a) and may express germinal center markers (CD10, BCL6). S100, CD1a, and CD207/lysozyme are negative. In some cases of

Figure 2. Differential diagnosis for histiocytic sarcoma. Histiocytic sarcoma (A) and classic Hodgkin lymphoma (B) may both show large atypical cells with prominent nucleoli in a mixed inflammatory background. Histiocytic sarcoma (C) and Rosai-Dorfman disease (D) both demonstrate histiocytic cells with inflammatory cells within their cytoplasm; however, histiocytic sarcoma tends to show cytophagocytosis rather than the true emperipolesis of Rosai-Dorfman disease. Histiocytic sarcoma (E) can include areas with relatively more uniform sized of histiocytoid cells that may resemble myeloid sarcoma. Myeloid sarcoma (F) has a less mature chromatin pattern, a more monotonous look, and less cytoplasm. Histiocytic sarcoma (G), like Langerhans cell sarcoma (H), demonstrates large pleomorphic atypical cells; however, the cells of histiocytic sarcoma are generally larger than those of Langerhans cell sarcoma and show less nuclear complexity (hematoxylin-eosin, original magnification ×400).
histiocytic sarcoma arising from a low-grade B-cell lymphoma, B-cell markers may be retained.

**Anaplastic Large Cell Lymphoma**

Anaplastic large cell lymphoma (ALCL) is an important differential diagnosis to consider, as many of the early reported “histiocytic sarcoma” or “malignant histiocytosis” cases were actually ALCL. Anaplastic large cell lymphoma is most commonly seen in the pediatric to young adult age groups, and commonly presents with lymph node enlargement. Sinusoidal lymph node involvement is often seen in ALCL as well as in histiocytic sarcoma. Skin, bone, and soft tissue are frequent extranodal sites. Anaplastic large cell lymphoma is composed of large cells with abundant basophilic cytoplasm, often with a prominent Golgi zone staining as a clear or more eosinophilic zone. Cells with horseshoe-shaped nuclei termed hallmark cells are seen in variable proportion in all cases. Multiple small basophilic nuclei may be seen, but prominent inclusion-like nuclei are uncommon. Plasma cells are often present, but neutrophils and eosinophils are usually sparse to absent. The lymphohistocytic variant of ALCL has a large number of reactive histiocytes that may obscure the malignant cells, but hallmark cells will still often form perivascular rosettes. Photomicrographs demonstrating the morphologic similarity between histiocytic sarcoma and anaplastic large cell lymphoma are shown in Figure 3, C and D. When the neoplastic cells of ALCL show histiocytic morphology, staining for other T-cell markers such as CD5 can be helpful. By definition, CD30 is diffusely positive with membranous and paranuclear staining. Cytotoxic markers such as perforin, granzyme, and T-cell intracellular antigen 1 (TIA-1) are positive, and CD3 and CD4 are variable. Most histiocytic markers should be negative. The majority of cases are epithelial membrane antigen (EMA) positive, so keratins are more useful in ruling out metastatic carcinoma. Characteristically, anaplastic lymphoma kinase (ALK)–positive ALCL demonstrates translocations involving the ALK gene, most commonly t(2;5); such translocations are not seen in histiocytic sarcoma.

**Interdigitating Dendritic Cell Sarcoma**

The neoplastic cells in interdigitating dendritic cell sarcoma may be spindled or epithelioid, and the epithelioid neoplastic cells may resemble those of histiocytic sarcoma. Interdigitating dendritic cell sarcoma can be associated with low-grade B-cell lymphoma, although much less commonly than histiocytic sarcoma. Architectural patterns include sheets, whorls, nests, and fascicles. Interdigitating dendritic cell sarcoma, too, commonly has inflammatory cells (small T cells +/- eosinophils and plasma cells) in the background. Although uncommon, hemophagocytosis and emperipolesis have been reported. Cases of interdigitating dendritic cell sarcoma involving lymph node may show a paracortical or sinusoidal distribution, like histiocytic sarcoma. The nuclei have vesicular chromatin with either small or prominent nucleoli, highly irregular and lobulated contours, and variable atypia. The neoplastic cells have abundant eosinophilic cytoplasm with indistinct cell borders, in contrast to the distinct cell borders of histiocytic sarcoma (Figure 3, E and F). Immunohistochemical evaluation generally demonstrates the neoplastic cells to be positive for S100 (intense, diffuse), fascin, HLA-DR, CD11c, and vimentin, and negative for CD1a and CD207/langerin. Although active interdigitating dendritic cells show membrane positivity for HLA-DR, exclusively globular/granular cytoplasmic reactivity is seen in neoplastic interdigitating dendritic cell proliferations. Expression of CD4, CD45, CD68, CD163, CD15, lysozyme, and sex-determining region Y–box 10 protein (SOX10) are variable. Useful features for the diagnosis of interdigitating dendritic cell sarcoma include presence of long dendritic processes, convoluted nuclei, and a predominance of S100 staining relative to CD68 staining.

**Follicular Dendritic Cell Sarcoma**

Follicular dendritic cell sarcoma is a rare neoplasm of the mesenchymal cells within germinal centers that can occur in nodal or extranodal locations. Follicular dendritic cell sarcoma commonly involves the head and neck region of adults, and may arise in the setting of hyaline vascular Castleman disease. It has a less aggressive course than the other entities described here. After surgery, median survival is 2.9 years, with 5-year recurrence-free survival of 34%. Adjuvant radiation and neoadjuvant chemotherapy do not clearly improve survival. Tyrosine kinase inhibitors and mammalian target of rapamycin (mTOR) inhibitors may play a role. When disease is localized, prognosis is better. Approximately 3% of patients have prior history of another lymphoma. Although high-grade follicular dendritic cell sarcoma may not have any pattern, fascicular, storiform, sheetlike, whorled, or jigsaw patterns are common. The neoplastic cells can be spindled or epithelioid, with oval or elongated nuclei, fine chromatin, small nucleoli, and indistinct cell borders. Multinucleated giant cells and nuclear pseudoinclusions can be frequent. Admixed small lymphocytes are often present and may aggregate around blood vessels. Photomicrographs demonstrating the morphologic similarity between histiocytic sarcoma and follicular dendritic cell sarcoma are shown in Figure 3, G and H. At least one follicular dendritic cell marker (CD21, CD23, CD35, clusterin, fascin) will be positive in follicular dendritic cell sarcoma. CD1a, CD207/langerin, S100, CD4, and CD45 are negative. CD20 and CD45 are positive in a small subset of cases. EMA, S100, and CD68 expression are variable. The Ki-67 proliferative index is 1% to 25%. As with other histiocytic and dendritic cell neoplasms, BRAF V600E mutations can be seen. Facchetti and colleagues reported that all follicular dendritic cell sarcoma cases they stained

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**Figure 3.** Differential diagnosis for histiocytic sarcoma. Histiocytic sarcoma (A) and diffuse large B-cell lymphoma (B) can occur as large cell transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma. In the past, some cases that were diagnosed as histiocytic sarcoma (C) were actually cases of anaplastic large cell lymphoma (D). Both entities may show histioid cytology: classic hallmark cells may be difficult to find, but tend to be located near blood vessels. Histiocytic sarcoma (E) shows a mixed inflammatory background similar to that of interdigitating dendritic cell sarcoma (F); however, interdigitating dendritic cell sarcoma tends to demonstrate more convoluted nuclei and less distinct cell borders. Histiocytic sarcoma (G) and follicular dendritic cell sarcoma (H) bear some superficial resemblance; however, follicular dendritic cell sarcoma often shows epithelioid to plump spindle cells with indistinct cell borders and background perivascular lymphoid aggregates (hematoxylin-eosin, original magnification x400).
were strongly positive for programmed death ligand-1 (PD-L1).

**Metastatic Carcinoma or Metastatic Melanoma**

Metastatic carcinoma or melanoma must be considered in the differential diagnosis. Clinical history of malignancy and immunohistochemical markers are helpful for accurate classification. Hemophagocytosis can be absent or inconspicuous in histiocytic sarcoma and can also be seen in other malignancies, including carcinoma. Cytokeratins and EMA are useful for the exclusion of metastatic carcinoma; however, EMA is also positive in some types of lymphoma. Melanoma is usually Melan-A and HMB-45 positive, but CD163 negative. CD68 (KP1 and PG-M1) stains a subset of melanomas and carcinomas.

**PROGNOSIS AND TREATMENT**

Most patients who die of disease have a short interval between diagnosis and death. Because of the rarity of histiocytic sarcoma, the optimal treatment strategy is not known. However, the most popular therapy for advanced histiocytic sarcoma appears to be cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone. The median overall survival for patients who receive adjuvant or neoadjuvant therapy is approximately 2.5 years, but there is no clear survival advantage. The prognosis is also not clearly better for patients with localized disease. Response to vemurafenib has been reported. Facchetti and colleagues reported that one-fourth of cases (3 of 12) showed strong and diffuse PD-L1 expression, suggesting that immunotherapy could potentially be helpful.

**CONCLUSIONS**

Histiocytic sarcoma is a rare histiocytic neoplasm that can arise as a result of transdifferentiation from a low-grade B-cell lymphoma like CLL/PLL, among other hematopoietic neoplasms. Although the morphologic differential is broad and includes histiocytic/dendritic cell neoplasms, myeloid neoplasms, lymphomas, carcinoma, and melanoma, knowledge of key morphologic and immunohistochemical features allows for accurate classification. In particular, CD163 is a helpful marker for histiocytic differentiation because of its increased specificity relative to CD68, which can also stain carcinoma and melanoma.

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**References**


