Histiocytic sarcoma, a rare malignant neoplasm showing morphologic and immunophenotypic features of histiocytes, is characterized typically by extranodal presentation and a dismal clinical course, particularly in patients with disseminated disease. A history of hematolymphoid disorder can be identified in a subset of patients, suggesting transdifferentiation of a preexisting hematolymphoid neoplasm in its pathogenesis. The differential diagnosis of histiocytic sarcoma includes various lymphomas, other histiocytic and dendritic cell neoplasms, carcinomas, melanomas, and pleomorphic sarcomas. Given its rarity and histologic overlap with diverse mimics, the diagnosis of histiocytic sarcoma can be extremely challenging. Recognition of morphologic clues, as well as judicious application of immunohistochemical markers to confirm its histiocytic lineage and to exclude mimics, is crucial for the diagnosis. Recent molecular studies by targeted next-generation sequencing identified recurrent alterations in chromatin regulators in the pathogenesis of histiocytic sarcoma and may suggest possible therapeutic targets. (Arch Pathol Lab Med. 2020;144:650–654; doi: 10.5858/arpa.2018-0349-RS)

Histologically, histiocytic sarcoma is composed of sheets of discohesive large polygonal cells with epithelioid-to-pleomorphic morphology, abundant eosinophilic to vacuolated or foamy cytoplasm, ovoid to irregularly shaped nuclei, and variably prominent nucleoli (Figure 1, A and B). Focal or foamy cytoplasm, ovoid to irregularly shaped nuclei, and variably prominent nucleoli (Figure 1, A and B). Focal

CLINICAL FEATURES

Histiocytic sarcoma presents with a wide age distribution and slight male predominance.1,5,8 While it occurs principally in adults, pediatric histiocytic sarcoma cases have been reported.2 Histiocytic sarcoma typically involves extranodal sites, including the gastrointestinal tract, superficial and deep soft tissue, lung, and nasal cavity.2 Primary histiocytic sarcomas of lymph nodes, skin, and brain have also been reported. Patients with histiocytic sarcoma have variable clinical presentations, ranging from localized disease with a solitary mass to widely disseminated disease. A subset of patients with histiocytic sarcoma has a history of hematolymphoid disorder such as follicular lymphoma,11 chronic lymphocytic leukemia/small cell lymphoma,13 marginal zone lymphoma,14 mantle cell lymphoma,15 hairy cell leukemia,15 and multiple myeloma.16 Association with germ cell tumor in the adult setting17 and autoimmune lymphoproliferative syndrome in the pediatric setting has also been reported.2 Histiocytic sarcoma is often very aggressive with a median survival of several months in patients with disseminated disease.2,5,8,16 Nonetheless, patients with localized histiocytic sarcoma may survive years after the initial diagnosis followed by aggressive clinical management.2,6,8

PATHOLOGIC FEATURES

Grossly, histiocytic sarcoma often presents as a fleshy mass with a well-circumscribed or an infiltrative border and variable hemorrhage or necrosis.2 Histologically, histiocytic sarcoma is composed of sheets of discohesive large polygonal cells with epithelioid-to-pleomorphic morphology, abundant eosinophilic to vacuolated or foamy cytoplasm, ovoid to irregularly shaped nuclei, and variably prominent nucleoli (Figure 1, A and B). Focal areas with spindled cells may be seen in a subset of cases. Mitotic activity and tumor necrosis are conspicuous, and a mixed background inflammatory infiltrate is often prominent.2,8 Hemophagocytosis may be present but is often subtle and obscured by the prominent inflammation.8 The histologic appearance of histiocytic sarcoma is otherwise nondistinctive, with significant morphologic overlap with diverse mimics (Table).
Patients with extranodal histiocytic sarcoma often undergo diagnostic fine-needle aspiration. The cytologic features include reniform nuclei with abundant vacuolated cytoplasm, multinucleated “monster” cells, histiocytoid cells with partially overlapping “Pac-Man”-like nuclei, a lymphoplasmacytic or neutrophilic background with lymphoglandular bodies, and emperipolesis. While diagnosing histiocytic sarcoma by cytomorphology alone can be extremely challenging and requires extensive immunohistochemical workup, fine-needle aspiration may be a useful tool to document disease recurrence.

**IMMUNOHISTOCHEMICAL FEATURES**

Immunohistochemistry is pivotal in the diagnosis of histiocytic sarcoma, both to confirm bona fide histiocytic differentiation with positive markers and to exclude morphologic mimics with negative markers.

For positive markers, most histiocytic sarcomas express CD68, CD163 (Figure 2, A), and PU.1 (Figure 2, B), with a subset of cases also expressing CD31, CD4 (cytoplasmic), and CD45RO. Expression of at least 2 of the following markers (CD68, CD163, CD4, and lysozyme) has been recommended as a diagnostic criterion in histiocytic sarcoma. Although α-1-antitrypsin, lysozyme, and CD68 (clones KP-1 and PGM-1) were used in earlier studies, each of these markers can be expressed in various neoplasms such as melanoma and is thus not specific for the histiocytic lineage alone. CD163 and PU.1 have been increasingly used in the diagnosis of histiocytic sarcoma and other histiocytoses. Compared to CD68, CD163 is more specific for the histiocytic lineage and for the diagnosis of histiocytic sarcoma. The transcription factor PU.1, a marker for the macrophage lineage, can be particularly helpful to visualize and confirm the nuclear immunoreactivity in the tumor cells amidst the extensive background inflammation. Aside from the markers discussed above, a subset of histiocytic sarcoma can also variably express CD15, CD45, human leukocyte antigen DR-isotype (HLA-DR), fascin, and factor XIIIa. In addition to expressing histiocytic markers, histiocytic sarcoma is expected to be negative for Langerhans cell (CD1a, langerin), follicular dendritic cell (CD21, CD35),

Figure 1. A, Histiocytic sarcoma, characterized by sheets of epithelioid tumor cells, with eosinophilic cytoplasm, variably prominent nucleoli, and admixed neutrophilic inflammation. B, Histiocytic sarcoma, showing pleomorphic tumor cells, with hyperchromasia, discohesion, and admixed chronic inflammation (hematoxylin-eosin, original magnification ×400 [A and B]).

Figure 2. A, Immunohistochemical stain for CD163 shows diffuse cytoplasmic immunoreactivity in histiocytic sarcoma. B, Immunohistochemical stain for PU.1 shows diffuse nuclear staining in histiocytic sarcoma (original magnification ×400 [A and B]).
Morphologic, Immunophenotypic, and Molecular Characteristics of Histiocytic Sarcoma and Its Major Differential Diagnoses

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Cytologic/Histologic Features</th>
<th>Immunohistochemical Markers</th>
<th>Molecular Features</th>
</tr>
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<tbody>
<tr>
<td>Histiocytic sarcoma</td>
<td>Multinucleated “monster” cells, histiocytoïd cells with “Pac-Man”-like nuclei, abundant vacuolated cytoplasm, mixed neutrophil-rich or lymphocyte-rich inflammatory background</td>
<td>At least 2 of the following: CD163, CD68 (KP-1 and PGM-1, the latter slightly more specific), CD4, lysozyme</td>
<td>Clonal IgH or TCR gene rearrangement (subset), alterations in MAP kinase pathway and epigenetic modifiers</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma</td>
<td>“Hallmark” cells (embryo-like nuclei with multiple basophilic nuclei), “donut” cells (pseudonuclear inclusion), marked pleomorphism, anisonucleosis</td>
<td>CD30, EMA, T-cell markers (variable), ALK (subset)</td>
<td>ALK rearrangement (subset)</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, NOS</td>
<td>Discohesion, anisonucleosis, variable pleomorphism</td>
<td>CD4 &gt; CD8; antigen loss frequent (CD7, CD5, CD4/ CD8, CD52)</td>
<td>Clonal TCR gene rearrangement, complex karyotype</td>
</tr>
<tr>
<td>High-grade B-cell lymphoma</td>
<td>Variable, with diffuse large atypical lymphoid cells</td>
<td>B-cell markers and germinatal center cell markers (variable)</td>
<td>IgH-BC16, IgH-BC12, MYC rearrangement, clonal IgH gene rearrangement</td>
</tr>
<tr>
<td>Hodgkin lymphoma, particularly the syncytial variant of classic type</td>
<td>Reed-Sternberg cells (binucleated with inclusion-like eosinophilic macronuclei, “owl’s eyes”) or Reed-Sternberg-like cell variants, eosinophilic-rich or lymphocytic-rich inflammatory background</td>
<td>CD30, CD15, PAX5, EBER (subset)</td>
<td>9p24 amplification at CD274 (PD-L1) locus</td>
</tr>
<tr>
<td>Myeloid sarcoma</td>
<td>Primitive to blast-like appearance (and a history of acute myeloid leukemia)</td>
<td>CD13, CD33, CD68, CD117, MPO (subset), cytoplasmic NPM1 (subset, skin)</td>
<td>Diverse, depending on the molecular subtypes of the underlying leukemia, NPM1 mutations</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis/sarcoma</td>
<td>Grooved, lobulated, vesicular nuclei, eosinophil-rich inflammatory background</td>
<td>S100, CD1a, langerin</td>
<td>BRAF V600E mutation (subset)</td>
</tr>
<tr>
<td>Follicular dendritic cell sarcoma</td>
<td>Isolated or syncytial sheets of spindle cells with intermediate-sized, ovoid vesicular nuclei, background of small lymphocytes</td>
<td>CD23, CD23, CD35, D2-40 (podoplanin)</td>
<td>BRAF V600E mutation (subset), alterations in NF-xB regulatory genes</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Intracytoplasmic pigment, prominent macronucleoli</td>
<td>S100, SOX10, HMB-45, MiTF, MART-1</td>
<td>BRAF V600E mutation (subset), alterations in MAP kinase pathway (subset)</td>
</tr>
<tr>
<td>Carcinoma, undifferentiated</td>
<td>Large epithelioid and round cells with necrosis and inflammation</td>
<td>Keratin, claudin-4, SMARCA4 (expression loss, subset)</td>
<td>Variable</td>
</tr>
<tr>
<td>Epithelioid angiosarcoma</td>
<td>Erythrophagocytosis, intracytoplasmic lumina, limited pleomorphism, less inflammation</td>
<td>CD31, CD34, ERG</td>
<td>Complex karyotype</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>Necrotic debris, palisaded by tumor cells</td>
<td>EMA, AE1/AE3, CD34, INI-1 (expression lost)</td>
<td>SMARC1/INI1 gene deletion</td>
</tr>
<tr>
<td>Pleomorphic rhabdomyosarcoma</td>
<td>Bizarre polygonal cells, tadpole-like cells, eosinophilic cytoplasmic inclusions, less inflammation</td>
<td>Desmin, Myf4 (myogenin), MyoD1</td>
<td>Complex karyotype</td>
</tr>
<tr>
<td>Unclassified pleomorphic sarcoma</td>
<td>Predominantly spindle cells with pleomorphism, hyperchromatic</td>
<td>SMA (variable), negative for most lineage markers</td>
<td>Complex karyotype</td>
</tr>
</tbody>
</table>

Abbreviations: ALK, anaplastic lymphoma kinase; CD, cluster of differentiation; EBER, Epstein-Barr virus–encoded ribonucleic acid; EMA, epithelial membrane antigen; ERG, Ets-related gene; HLA-DR, human leukocyte antigen DR-isotype; HMB-45, human melanoma black-45 antigen; IgH, immunoglobulin heavy chain; INI-1, integrase interactor 1; MAP, mitogen-activated protein; MART-1, melanoma-associated antigen recognized by T cells-1; MiTF, microphthalmia-associated transcription factor; MPO, myeloperoxidase; MyoD1, myoblast determination 1; NF-JB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOS, not otherwise specified; NPM1, nucleophosmin 1; PAX5, paired box 5; PD-L1, programmed cell death ligand-1; PGM-1, phosphoglucomutase-1; SMA, smooth muscle actin; SMARCA4, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily a, member 4; SOX10, sex-determining region Y-box 10; TCR, T-cell receptor.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of histiocytic sarcoma is notably broad and includes diverse neoplasms dominated by a large epithelioid or pleomorphic cell pattern, including various myeloid cell (CD13, MPO), melanocytic (SOX10, HMB-45, MART-1), epithelial (keratin, EMA), vascular (ERG), and specific B-cell and T-cell (CD20, PAX5, CD3) markers (Table).
lymphomas (such as anaplastic large cell lymphoma, large B-cell non-Hodgkin lymphoma, and Hodgkin lymphoma), poorly differentiated or undifferentiated carcinomas, melanomas, sarcomas (such as epithelioid angiosarcoma, epithelioid sarcoma, pleomorphic rhabdomyosarcoma, and unclassified pleomorphic sarcomas), and dendritic cell tumors (such as follicular dendritic cell sarcoma). In addition, histiocytic sarcoma can be mistaken for other histiocytic diseases like Langerhans cell histiocytosis and Langerhans cell sarcoma. Despite morphologic similarities, there are histomorphologic, immunohistochemical, and molecular features that can provide distinction between histiocytic sarcoma and its mimics.2,16 A summary of differential diagnoses of histiocytic sarcoma is provided in the Table.

Anaplastic large cell lymphoma (ALCL) is characterized by “hallmark” cells, with embryo-like nuclei and multiple prominent nucleoli. A subset of ALCLs is anaplastic lymphoma kinase (ALK) positive, harboring ALK gene rearrangement and showing ALK protein overexpression.20 Both ALK-positive and ALK-negative ALCLs can be confused with histiocytic sarcoma owing to overlapping morphologic features. ALCL may express CD68, and histiocytic sarcoma can express CD4 and CD43, further contributing to diagnostic confusion.21 Demonstration of clonal TCR gene rearrangement along with a collection of other findings, including the expression of additional T-cell markers (other than CD4 and CD43) and the absence of CD163 and PU.1, can distinguish T-cell lymphomas (like ALCL and peripheral T-cell lymphomas, not otherwise specified) from histiocytic sarcoma. High-grade large B-cell lymphomas show variably marked pleomorphism and can be easily mistaken for histiocytic sarcoma; yet, most large B-cell lymphomas are positive for B-cell lineage markers that are not expressed in histiocytic sarcoma. Although nodular sclerosis classic Hodgkin lymphoma, particularly the syncytial variant, may mimic histiocytic sarcoma, the neoplastic cells in Hodgkin lymphoma do not express histiocytic markers. While histiocytic sarcoma and myeloid sarcoma both express histiocytic markers with significant immunophenotypic overlap, histiocytic sarcoma is typically more morphologically pleomorphic and is not associated with a history of acute monocytic leukemia. The diagnosis of myeloid sarcoma can be aided by myeloid markers such as CD13, CD33, and myeloperoxidase.3

Poorly differentiated or undifferentiated carcinomas with anaplastic features can share morphologic overlap with histiocytic sarcoma; however, expression of epithelial markers including keratins and claudin-4 would strongly favor carcinoma and exclude histiocytic sarcoma. Melanoma can be dominated by an epithelioid-to-pleomorphic histology with prominent nucleoli, reminiscent of histiocytic sarcoma. While a subset of histiocytic sarcomas can be positive for the S100 protein, they are consistently negative for other melanocytic markers such as HMB-45 and SOX10.

Since both histocytes and histiocytic sarcoma often express the endothelial marker CD31,2,22 this can lead to confusion with angiosarcoma—a known diagnostic pitfall. Epithelioid angiosarcoma typically displays epithelioid to pleomorphic tumor cells with amphophilic cytoplasm, variable vasoformative features, and expression of additional vascular markers such as ERG and CD34. On the other hand, the combination of CD31 expression with hematopoietic/histiocytic markers (LCA, CD4, CD68, CD163, PU.1) in the absence of other vascular markers (CD34, ERG) in large epithelial cells should instead suggest histiocytic sarcoma. Epithelioid sarcoma can mimic histiocytic sarcoma with an epithelioid-to-pleomorphic morphology and prominent tumor necrosis. However, epithelioid sarcoma is characterized by immunoreactivity for AE1/AE3 keratin, EMA, and/or CD34, along with loss of SMARCB1/INI-1 expression,23 which are not seen in histiocytic sarcoma. Pleomorphic rhabdomyosarcoma demonstrates bizarre polygonal cells but, unlike histiocytic sarcoma, shows expression for desmin, Myf4 (myogenin), and MyoD1.24 Follicular dendritic cell sarcoma is characterized by sheets and syncytial whorls of tumor cells with interspersed background lymphocytes and is positive for CD21, CD23, CD35, and D2-40,25,26 the expression of which are absent in histiocytic sarcoma.

Since histiocytic sarcoma typically shows unequivocal features of malignancy with numerous mitoses, necrosis, and cellular pleomorphism, its distinction from other histiocytoses and neoplasms of the macrophage lineage such as Erdheim–Chester disease, juvenile xanthogranuloma, and sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) is often straightforward.3 Both Langerhans cell histiocytosis and Langerhans cell sarcoma show characteristic grooved nuclei with immunoreactivity for S100, CD1a, and langerin. While a minor subset of histiocytic sarcoma may express S100 protein or CD1a, the expression is typically patchy.2,13 Furthermore, prominent eosinophilic infiltrate, a helpful diagnostic clue in Langerhans cell histiocytosis and Langerhans cell sarcoma, is not a feature in histiocytic sarcoma.

MOLECULAR FEATURES

Histiocytic sarcoma has been suggested to arise from transdifferentiation of preexisting hematolymphoid neoplasms in a subset of patients, as their histiocytic sarcomas and hematolymphoid neoplasms share identical molecular alterations and thus appear clonally related.11–15 Immunoglobulin H (IgH)–BCL2 fusion has been detected in both the histiocytic sarcoma and follicular lymphoma in patients harboring both diseases.11,12 Identical immunoglobulin gene rearrangement has been detected in the histiocytic sarcoma and chronic lymphocytic leukemia/small cell lymphoma in 1 patient with both diseases.13 Cyclin D1–IgH fusion has been reported in both the histiocytic sarcoma and mantle cell lymphoma in 1 patient.14 BRAF mutation V600E has been identified in both the histiocytic sarcoma and hairy cell leukemia in 1 patient with coexisting diseases, again indicating common genetic origin.15

Recently, a subset of histiocytic sarcomas has been reported to harbor alterations in BRAF, including V600E15,16 and non-V600E mutations.27 In addition, 3 cases of histiocytic sarcoma have been reported to harbor recurrent mutations in KMT2D, a gene involved in epigenetic regulation and commonly mutated in follicular lymphomas.18 A targeted next-generation sequencing study of 18 histiocytic sarcomas has identified recurrent mutations in the MAP kinase pathway, including KRAS, NRAS, and MAP2K1 activating mutations, along with mutations in KMT2D and ARID1A.28 The findings of MAP kinase alterations in histiocytic sarcoma are reminiscent of the recent comprehensive molecular profiling in Langerhans cell histiocytosis and Erdheim–Chester disease, in which recurrent activating mutations in BRAF, MAP2K1, and ARAF as well as kinase fusions in BRAF, ALK, and NTRK1 are identified.29 Overall, the recent molecular discoveries
suggest that alterations in the MAP kinase pathway and chromatin regulation underlie the pathogenesis of a variety of histiocytic neoplasms, including histiocytic sarcoma, and may represent future therapeutic targets.

**CONCLUSIONS**

Given its rarity and histologic overlap with diverse mimics, the diagnosis of histiocytic sarcoma can be extremely challenging. Recognition of morphologic clues, as well as judicious application of immunohistochemical markers to confirm histiocytic differentiation and exclude mimics, is crucial. The recent insights on the recurrent genetic alterations in the MAP kinase pathway and histioblastic types suggest therapeutic targets, some of which are currently under active clinical investigation and may help in the treatment of this aggressive disease.

**References**