

HISTIOCYTIC SARCOMA – Karen L. Chang, M.D.

A simplistic model of the four functional histologic compartments of a lymph node and the corresponding predominant immunologic cell components includes: 1) the follicle or germinal center (dendritic reticulum cells, lymphoid cells, tingible body macrophages); 2) medullary cords (plasma cells, lymphoid cells, macrophages, mast cells); 3) paracortex (interdigitating cells, epithelioid venules, T-lymphocytes); and 4) sinuses (macrophages, B-cells). One of the primary functions of lymph nodes is to process antigens.

Normal histiocytes are defined as having a high content of lysosomal enzymes, phagocytosing capabilities, and derivation from the bone marrow stem cells (granulocyte-macrophage colony-forming units). Histiocytes are mobile and circulating in the sinuses of lymph nodes, tonsils, and spleen. Histiocytes that are “fixed” in tissue are called macrophages. Whether freely mobile or fixed, histiocytes have large oval nuclei with bland nuclear chromatin and a moderate to abundant amount of cytoplasm, depending on their functional state.

Histiocytes are primarily antigen-processing cells (phagocytosis), whereas dendritic cells are primarily antigen-presenting cells. The cells in this latter category include Langerhans cells, follicular dendritic (or dendritic reticulum) cells, interdigitating dendritic (interdigitating reticulum cells), and indeterminate cells.

Tumors derived from the histiocytic and dendritic cells are listed in Table 1, which uses the WHO Classification of histiocytic and dendritic cell neoplasms.

Definition: Histiocytic sarcoma is defined in the WHO Classification as a neoplastic proliferation with features of histiocytes.(1-4) Extramedullary myeloid tumors with monocytic differentiation (e.g. acute monoblastic leukemias) and dendritic cell neoplasms are excluded. Histiocytic sarcoma has been previously called “true histiocytic lymphoma” and even more remotely “malignant histiocytosis.”

The term “malignant histiocytosis” is no longer used because most earlier reported cases of that entity were subsequently shown to be lymphomas, generally of T-cell origin, including many cases of anaplastic large cell lymphoma, which was only later recognized as a true entity.(5-8)

Epidemiology: Histiocytic sarcoma accounts for <1% of all hematolymphoid neoplasms and occurs most commonly in adults, equally between men and women.(9) Infants and children may also be affected. Some cases of histiocytic sarcoma are associated with or occur subsequent to a non-Hodgkin lymphoma.(10,11) A subset of histiocytic sarcomas is associated with primary mediastinal nonseminomatous germ cell tumors, in particular malignant teratoma with or without yolk sac differentiation.(12,13,14) In addition to the mediastinal neoplasms, rare cases of malignant histiocytosis have also been described in patients with primary gonadal germ cell tumors.(15,16) Interestingly, the risk of developing a hematologic disorder in patients with primary mediastinal nonseminomatous germ cell tumors is statistically significantly higher than in the general population. The hematologic malignancies often occur within one year of the germ cell tumor diagnosis and adversely affect prognosis. Many of the hematologic neoplasms show megakaryocytic lineage (acute megakaryoblastic leukemia, myelodysplasia with abnormal megakaryocytes, or idiopathic/essential thrombocytosis), but cases of acute lymphocytic leukemia or other acute myeloid leukemia, systemic mastocytosis, and histiocytic sarcoma have also been described.(14,17,18,18,19) Investigators hypothesize the association results from the divergent differentiation of a shared multipotential progenitor cell into both a hematologic

malignancy and a germ cell tumor.(14,17,19)

Other entities historically associated with so-called malignant histiocytosis include *histiocytic medullary reticulosis* and *regressing atypical histiocytosis*. Histiocytic medullary reticulosis, an entity first described in 1939, have been found to comprise a heterogeneous group of diseases, including Hodgkin's disease, anaplastic large cell lymphoma, peripheral T cell lymphoma with or without hemophagocytosis, and Lennert lymphoma, as well as hyperimmune reactions.(20,21) Cases of *regressing atypical histiocytosis* are been reclassified as lymphomatoid papulosis/anaplastic large cell lymphoma, cutaneous type, and not histiocytic sarcoma.(22)

Etiology: No precursor lesions and no etiologic agents have been uncovered.

Clinical features: Patients generally present with fever, fatigue, weight loss, and weakness. Physical findings usually include lymphadenopathy and may include hepatosplenomegaly or splenomegaly alone, or skin lesions (range from solitary tumors to innumerable lesions on the trunk and extremities).(4,23-25) Some patients may present with intestinal obstruction. The bone may show lytic lesions. One case has been described as primary in the central nervous system.(26)

Morphology: Lymph nodes involved by histiocytic sarcoma may show partial or complete effacement by a proliferation of cytologically malignant cells resembling histiocytes.(4) Visceral organ involvement may show a sinusoidal pattern. The extent of mitotic activity closely parallels the degree of cellular pleomorphism, which is quite variable. A variable number of host cells are present, including small lymphocytes, plasma cells, benign histiocytes, and eosinophils. The malignant cells have large, eccentrically-placed, oval nuclei with vesicular chromatin and a prominent single irregular nucleolus. The nucleus may appear grooved. Cytoplasm is abundant and eosinophilic, and may be foamy or vacuolated. Large multinucleated tumor cells and multiple nucleoli may also be seen. Hemophagocytosing tumor cells are extremely rare. Spindle cell sarcoma-like areas are present in some tumors. The tumor cytology and architecture is not particularly unique and thus, immunophenotypic and molecular studies are absolutely essential for diagnosis.

Ultrastructure (Table 2): Ultrastructural features of the neoplastic cells include abundant cytoplasm with numerous lysosomes. Birbeck granules and cellular junctions are not seen.

Immunophenotype (Table 3): One should see immunophenotypic evidence of histiocyte lineage, including expression of CD68, CD163, CD14, CD4, CD11c, lysozyme, and alpha-1 antitrypsin. The granular staining pattern of lysozyme, with Golgi region accentuation, may offer a clue that one is dealing with a histiocytic sarcoma and not other neoplasms, which usually show more diffuse staining. CD45, CD45RO, and HLA-DR are usually positive in histiocytic sarcoma. S100 may also be positive and rare cases are CD56-positive.(4,27,28) By definition, markers of B-lineage and T-lineage are negative, as are markers of dendritic cells, CD1a, CD34, CD30, HMB-45, myeloperoxidase, epithelial membrane antigen, and keratins.(9,23,27,29) The Ki-67 index varies from 10% to 90% of tumor cells.

Genetics/molecular findings (Table 2): In many cases, immunohistochemistry may not offer a definitive answer to the lineage of the neoplasm and thus, one must resort to molecular studies. Most pathologists require the absence of clonal immunoglobulin and T cell receptor antigen genes for the diagnosis of histiocytic sarcoma.(4,5,30,31) No consistent cytogenetic abnormalities have been found in studies using cases fulfilling modern immunophenotypic criteria for the diagnosis of histiocytic sarcoma.

Postulated cell of origin: Histiocytic sarcoma cells have similar morphologic and immunophenotypic features to those of mature tissue histiocytes.

Clinical course: Many cases of histiocytic sarcoma have an aggressive clinical course, with most dying from progressive disease within the first year.(24,27,32) However, a subset of patients who present with clinically localized, resectable disease treated with surgery alone, have a favorable long-term outcome, with follow-up times ranging from 13 to 92 months. Although there are no well-established prognostic markers, tumor size may correlate with prognosis.

Differential diagnosis (Table 4): The differential diagnosis of histiocytic sarcoma includes anaplastic large cell lymphoma, B- or T-cell large cell lymphomas (particularly those associated with benign erythrophagocytosis), anaplastic carcinomas with hemophagocytosis, follicular dendritic cell neoplasms, hepatosplenic T-cell lymphoma, and malignant melanoma. By adhering to strict clinical, immunophenotypic and molecular criteria for histiocytic sarcoma, one may exclude these other anaplastic tumors.(4,33-35) Myeloid sarcoma (particularly those with monoblastic differentiation) also may be confused with histiocytic sarcoma, but the former has smaller, more monomorphic tumor cells and may be CD34-positive.(27) Benign entities with a proliferation of histiocytes, such as infection-associated hemophagocytic syndrome, familial hemophagocytic lymphohistiocytosis, and storage diseases such as Gaucher or Niemann-Pick disease, can be generally excluded because of malignant cytologic features.(33,34)

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Table 1. WHO Classification of Tumors of Histiocytic and Dendritic Cells

- A. Macrophage/histiocytic neoplasm
 1. Histiocytic sarcoma
- B. Dendritic cell neoplasms
 1. Langerhans cell histiocytosis
 2. Langerhans cell sarcoma
 3. Interdigitating dendritic cell sarcoma/tumor
 4. Follicular dendritic cell sarcoma/tumor
 5. Dendritic cell sarcoma, not otherwise specified

Table 2. Ultrastructural, Enzyme Immunohistochemistry and Molecular Characteristics of Histiocytic Neoplasms

	Ultrastructure				Enzyme Immunohistochemistry				Molecular			
	Desmosomes	Birbeck Granules	Lysosomes	Cytoplasmic Processes	Alpha naphthyl Acetate Esterase	Naphthol AS-D Chloracetate Esterase	Lysozyme	Alpha-Antitrypsin	Recurring Cytogenetic Abnormalities	IgH	TCR	EBV
Langerhans' cell histiocytosis	-	+	-	-	+	-	-	-	-	-	-	-
Histiocytic sarcoma	-	-	Numerous	-	+	-	+	+	-	-	-	-
Follicular dendritic cell sarcoma/tumor	Numerous	-	Rare	Numerous	-	-	-	-	-	-	-	-
Interdigitating dendritic cell sarcoma	Not well-formed, one sees numerous complex interdigitating cell processes instead	-	Scattered	-	+	-	+	-	-	-	-	-

Table 3. Immunohistochemical Characteristics of Histiocytic Neoplasms

Immunohistochemistry														
	CD1	CD3	CD20	CD21	CD23	CD30	CD34	CD35	CD45	CD56	CD68	CD163	S-100	Lysozyme
Langerhans' cell histiocytosis	+	-	-	-	-	-	-	-	-	-	+	+	+	+/-
Histiocytic Sarcoma	-	-	-	-	-	-	-	-	Usually +	Rare +	+	+	+/-	+ (granular)
Follicular dendritic cell sarcoma/tumor	-	-	Rare +	+	+	-	-	+	Weakly +	-	+/-	+/-	Rare +	-
Interdigitating dendritic cell sarcoma	-	-	-	-	-	-	-	-	+	?	+/-	+	+	+

Table 4. Differential Diagnosis of Histiocytic Neoplasms

<u>Histiocytic neoplasm</u>	<u>Differential diagnosis</u>	<u>Useful morphologic features</u>	<u>Useful ancillary test results</u>
Histiocytic Sarcoma			
	Anaplastic large cell lymphoma	Sinusoidal pattern of involvement; “hallmark” cells	Immunohistochemistry: CD30+, alk+/- FISH or molecular studies: t(2;5)
	T-cell lymphoma with erythrophagocytosis	Large histiocytes with emperipolesis	Immunohistochemistry: Tumor cells CD68- Molecular studies: T-cell gene arrangements are present
	Myeloid sarcoma	Monomorphic tumor cells with fine blastic chromatin	Immunohistochemistry: Strong myeloperoxidase positivity
	Malignant melanoma	Fine brown pigment in cytoplasm	Immunohistochemistry: HMB-45+, Melan A+
Follicular Dendritic Cell Sarcoma/Tumor			
	Interdigitating dendritic cell sarcoma/tumor		Immunohistochemistry: Lacks CD21, CD35, and CD1 expression Electron microscopy: lacks desmosomes
	Thymoma	Hassall’s corpuscles	Immunohistochemistry: Keratin +
	Spindle cell carcinoma	Tight clustering of tumor cells	Immunohistochemistry: Keratin +
	Melanoma	Fine brown pigment in cytoplasm	Immunohistochemistry: HMB45+, Melan A+
Interdigitating dendritic cell sarcoma/tumor			
	Follicular dendritic cell sarcoma/tumor	Small reactive lymphocytes interspersed throughout neoplasm	Immunohistochemistry: CD21+, CD35+, may be EMA+; small reactive lymphocytes may be B-lineage Electron microscopy: numerous desmosomes
	Langerhans’ cell sarcoma	Oval indented nuclei	Immunohistochemistry: S100+/CD1+; Electron microscopy: Birbeck granules
	Pleomorphic large cell lymphoma	Small reactive lymphocytes interspersed throughout neoplasm	Immunohistochemistry: B or T lineage markers are present; small reactive lymphocytes are T-lineage Molecular studies: IgH or TCR gene rearrangements
	Fibroblastic reticular cell tumor		Immunohistochemistry: S100-; positive for smooth muscle actin and desmin

Table 5. Pearls and Pitfalls in the diagnosis of histiocytic lesions other than Langerhans' cell histiocytosis

1. These are extremely uncommon lesions.
2. If you identify an S100-positive lesion in the lymph node, be sure to exclude metastatic malignant melanoma first, as melanoma is far more common than a histiocytic lesion.
3. If you have excluded melanoma in an S100-positive lesion, consider Langerhans' cell histiocytosis first because that is more common than the other histiocytic/dendritic lesions.
4. If you have a limited amount of tissue, immunohistochemistry is far more useful than molecular, flow, or cytogenetic study in the classification of these lesions.
5. The four most discriminatory immunohistochemical stains are S100, CD1, CD21, and CD35. Lysozyme, CD68, and EMA are also very useful.