

Society for Hematopathology: Identifying and Understanding Histiocytic and Dendritic Cell Neoplasms

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HISTORICAL OVERVIEW OF THE HISTIOCYTIC DISORDERS

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Our concepts of the histiocytic disorders have significantly changed over the past 30 years. Many reactive and neoplastic proliferations once thought to be of histiocytic derivation are now recognized as proliferations of T and B lymphocytes. We also have a better understanding of the functional complexity of the histiocytic and reticulum cell system. These concepts have been applied to modern classification schemes of histiocytic and reticulum cell proliferative disorders.

Reticulum cell sarcoma was a term first used by both Oberling (1928) and Roulet (1930) to describe aggressive tumors of the lymphoreticular system. Gall and Mallory (1942) recognized two variants: one composed of highly undifferentiated cells of presumptive stem cell origin and a second composed of more differentiated cells with the capability to migrate and perform phagocytosis. Rappaport, in his fascicle published in 1966, proposed that the "stem cell lymphomas" be termed *undifferentiated* and that the more differentiated lymphomas be called *histiocytic*. The identification of reactive histiocytes containing apoptotic debris and/or red blood cells had been used to infer a histiocytic origin for the background neoplastic cells. However, the application of modern immunologic concepts demonstrated that nearly all such "reticulum cell sarcomas" were of lymphoid derivation and of B-cell origin in the majority of cases.

Histiocytic medullary reticulosis (Robb-Smith, 1939) was another disorder once believed to be a neoplastic proliferation of histiocytes. These patients had a fulminant clinical course with widespread erythrophagocytosis throughout the reticuloendothelial system. It is not surprising that this uncontrolled phagocytic activity was thought to be the manifestation of a malignant population. However, this disorder is now recognized as a hemophagocytic syndrome (HPS). Deregulated cytokine and chemokine production has been implicated in the pathogenesis of HPS. However, the histiocytes that exhibit the florid phagocytic activity are benign. Recent studies have found increased expression of MIP-1 α in all patients with HPS, regardless of the underlying cause. Both neoplastic and infectious processes can precipitate an HPS, with T cells and NK cells being at the heart of the cytokine cascade. Many of the associated T-cell lymphomas are Epstein-Barr virus (EBV) associated, and acute or chronic EBV infections can also lead to HPS.

Histiocytic cytophagic panniculitis is a related process, also thought to be an HPS associated with a particular type of T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma. Histiocytic proliferation can be seen in the subcutaneous infiltrates, usually related to fat necrosis. However, hemophagocytosis is usually inconspicuous in this site. As with other HPS, hemophagocytosis is seen in the bone marrow, splenic red pulp, and hepatic and lymphoid sinuses. Intravascular lipid has been implicated in increased histiocytic activation in patients who are receiving hyperalimentation.

Most anaplastic large cell lymphomas were formerly diagnosed as malignant histiocytosis. The neoplastic cells selectively infiltrated lymphatic sinuses, and this dissemination pattern was taken as evidence of a histiocytic derivation. Today, we still do not understand the pathophysiologic basis of the sinusoidal infiltration, but the neoplastic cells have been shown to be of T-cell genotype, with a T- or null-cell immunophenotype. Anaplastic large cell lymphoma has been defined as a distinct clinicopathologic entity associated with overexpression of the ALK tyrosine kinase, usually as a consequence of the t(2;5). ALK-negative cases with a similar morphology and immunophenotype also exist and may represent a different but related entity.

Current classification schemes for histiocytic and reticulum cell proliferative disorders distinguish between phagocytic histiocytes (antigen-processing cells) and dendritic cells (antigen-presenting cells). True histiocytic malignancies are rare, with acute monocytic leukemia being the most common disorder derived from cells with phagocytic potential. Histiocytic sarcomas are much more infrequent. Neoplasms derived from dendritic cells include Langerhans' cell histiocytosis, interdigitating reticulum cell sarcoma, fibroblastic reticulum cell sarcoma, and follicular dendritic cell tumor/sarcoma. However, precise subclassification of many dendritic cell tumors often is difficult, because of imprecision in the antigenic phenotype. The World Health Organization's classification of hematopoietic and lymphoid neoplasms will include the above entities, with the exception of the recently described fibroblastic reticulum cell sarcoma. This neoplasm would be classified as dendritic cell tumor, not otherwise specified.

BIOLOGY OF HISTIOCYTIC AND DENDRITIC CELLS

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Histiocytes (macrophages) are derived from hematopoietic stem cells via monocyte-macrophage progenitor cells, monoblasts, promonocytes, and monocytes. They represent the tissue component of the mononuclear phagocyte system, which is present in all organs. Histiocytes express the surface markers HLA-DR, CD45, CD11c, CD13, CD14, CD33, Mac387, and CD4, as well as the lysosomal markers CD68 and lysozyme. They have specific receptors that react with various types of immunoglobulins, complement, glycoproteins, transferrin, lipoproteins, peptides, coagulation factors, hormones, and cytokines, including TNF family proteins, interleukin-1, interferon- γ , and M-CSF. They internalize substances by pinocytosis or phagocytosis, in general fusing the internalized vesicles with lysosomes. They respond to a number of chemotactic factors, including human (particularly C5a) and foreign substances, with motility supported by an actin-based cytoskeletal apparatus. They produce a wide range of substances, most notably enzymes (including lysozyme, neutral proteases, and acid hydrolases), complement factors, coagulation factors, reactive oxygen and nitrogen species, bioactive lipids, and numerous cytokines and growth factors. They mediate resistance to intracellular microorganisms and tumors through nonimmunologic mechanisms. They gain enhanced resistance to intracellular microorganisms through a process called activation, induced by lymphokines, particularly interferon- γ . They also play an important role in the recognition and clearance of apoptotic cells.

Dendritic cells seem to comprise at least two lineages, including myeloid and lymphoid. Myeloid dendritic cells are derived from CD34+ progenitors in the bone marrow that differentiate under stimulation from GM-CSF, TNF- α , and other factors into immature dendritic cells (Langerhans' cells). Langerhans' cells possess Birbeck granules and express CD1 and S100 protein but only low levels of accessory molecules that mediate binding and stimulation of T cells. They have abundant MHC II products within intracellular compartments, which represent efficient antigen processing and presentation machines. As these cells respond to inflammatory-induced cytokines or microbial substances, they become mature dendritic cells with abundant surface MHC II. They lose their Birbeck granules and CD1 and migrate through the lymph system (as veiled cells) to the paracortical region of lymph nodes. There, they become interdigitating cells, which, through surface MHC-peptide complexes, the expression of T-cell stimulatory molecules (e.g., CD40, CD86), and the secretion of an array of chemokines, leads to the initiation of strong cellular immunity. Their ultimate fate is cell death by apoptosis, accompanied by their phagocytosis and processing by lymphoid dendritic cells. An alternate pathway has been proposed for myeloid dendritic cells. In this hypothesis, a CD34+, CD45- marrow cell or a CD14+ peripheral blood monocyte, under the influence of GM-CSF, TNF- α , and IL-4, differentiates into a mature dendritic cell that may circulate in the blood or home to the peripheral interstitial spaces (a subset of which may be Factor XIIIa+) or sites of inflammation. It is thought that these cells have a role in humoral immunity. It is possible that these cells, upon contact with antigen, may become the antigen-transporting cells that travel through afferent lymph vessels into the lymph node and probably become follicular dendritic cells (now thought, but not yet proved, to be bone marrow-derived). Follicular dendritic cells form a reticulum meshwork within germinal centers, retaining immune complexes on their cell surface. They lack CD45 but express the complement receptors CD21 and CD35. They are intimately involved in memory cell formation and affinity maturation of follicular B cells. A second major lineage of dendritic cells is the lymphoid dendritic cells. These cells are derived from lymphoid-committed bone marrow stem cells, which migrate to the thymic medulla and, under the influence of IL-3, differentiate into dendritic cells that migrate to the lymph node. The latter may arrive through high endothelial venules as plasmacytoid T cells. With further maturation, these lymphoid dendritic cells are thought to reside in the T-cell areas and may be indistinguishable from myeloid-derived interdigitating cells. These cells may be responsible for immune tolerance through immune regulation and/or deletion via their uptake of self-peptides captured by the uptake of apoptotic myeloid dendritic cells.

Another reticular cell of the lymph node is the fibroblastic reticular cell. In contrast to the other cells described, these cells do not share a bone marrow origin and probably represent myofibroblastic structural elements, without function in the immune system.

HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS: A NEW APPROACH FROM THE INTERNATIONAL LYMPHOMA STUDY GROUP (ILSG)

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Neoplasms of histiocytes and immune accessory (dendritic) cells are rare, and their phenotypic and biologic definition is incomplete. Seeking to identify and further define distinct disease entities, the International Lymphoma Study Group (ILSG) stained 61 tumors of suspected histiocytic, accessory cell type with antibodies to histiocytic (CD68, lysozyme), Langerhans' cell (CD1a, S-100), and follicular dendritic cell (FDC; CD21, CD35, CNA42) antigens, among other markers. This analysis revealed four major groups (one histiocytic and three accessory cell types) defined primarily by immunophenotype and further refined by histologic and electron-microscopic (EM) examination:

1. True histiocytic malignant tumor (THMT) with 18 cases that were CD68⁺, lysozyme⁺, S-100 protein[±], CD45[±], CD1a⁻, and FDC antigen⁻. The median age was 46 years. Presentation was predominantly extranodal (72%) with high mortality (58% died of disease [DOD]). Three had systemic involvement consistent with malignant histiocytosis.
2. Langerhans' cell tumor (LCT) with 26 cases that were CD1a⁺, S-100 protein⁺, CD68[±], lysozyme[±], CD45[±], and FDC antigen⁻. By EM, 73% had Birbeck granules. The median age was 36 years with frequent extranodal involvement (88%). An ascending scale of atypia was found: 11 cases with no atypia (LCT.A/typical), 6 with some atypia (LCT.B/atypical), and 9 with frankly malignant cytologic features (LCT.C/LC sarcoma). Correlating with increasing cytologic atypia was increasing disease dissemination (e.g., Stages C and D at 50% in LCT.A, 83% in LCT.B, and 89% in LCT.C). Among LCT.A and B, 31% DOD, whereas among LCT.C, 50% DOD, suggesting a correlation between sarcomatous morphology and poor outcome. Four patients had systemic involvement typical of Letterer-Siwe disease.
3. Follicular dendritic cell tumor/sarcoma (FDCT): 13 cases had fusiform, whorled cells with strong dendritic cell-associated markers (FDC+[CD21,CD35,CNA42]), variable S-100, absent Langerhans' cell-associated antigen (CD1a⁻), and weak histiocytic markers (variable CD68 and near-absent lysozyme). By EM, 89% had desmosomes. These patients were adults (median age, 65 years) with predominantly localized disease (75%) and low mortality (9% DOD).
4. Interdigitating dendritic cell tumors/sarcoma (IDCT): four cases with fusiform, whorled cells that strongly expressed S-100 but lacked CD1a and germinal center-associated FDC antigens and on EM showed complex interdigitating cellular junctions. Characteristic paracortical nodal involvement occurred in two cases. IDCT were in adults (median age, 71 years) with predominantly localized nodal disease (75%) with low mortality (0% DOD).

We conclude that a simpler, more assured classification of histiocytic and accessory cell neoplasms is possible. This assurance is gained by integration of new phenotypic data with light microscopy and EM. The specificity of each entity is increased on the basis of the amalgamation of morphologic, phenotypic, and ultrastructural features.

PEDIATRIC PERSPECTIVES ON HISTIOCYTIC AND DENDRITIC CELL PROLIFERATIVE DISORDERS

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Systemic or multifocal proliferative disorders involving histiocytes of dendritic or macrophage phenotype are most commonly encountered in early childhood and still cause substantial morbidity and mortality. The nature of these conditions is poorly understood, particularly whether they are neoplastic, and their biologic potential for progression and response to therapy is not always predictable. Because of the extreme rarity of these conditions, there is only limited *in situ* phenotyping available.

Langerhans' cell histiocytosis (LCH) is the best known of the dendritic cell proliferative disorders and is now diagnosed by identifying the LCH cell that has a characteristically folded nucleus and is CD1a⁺, S100⁺, Lag⁺, and LG⁺ (EM) in an appropriate clinical setting. No consistent genetic marker has been identified, but all lesions tested to date have been clonal. Diagnostic problems are encountered in lesions that are regressing or have been treated and in which the diagnostic cell is no longer demonstrable (bone, liver) and when lesions are not the result of

direct cellular infiltration (cerebellum). There are clear cases of histiocytosis in which the lesional dendritic cells are phenotypically and morphologically different from those of LCH. Dendritic cell histiocytomas and the rare, systemic dendritic cell histiocytoses can have a variable phenotype that is generally CD68⁺ and HLA-DR⁺ with variable staining for CD1a, S100, fascin, and FXIIIa. Local progression and local recurrences have been seen, which is different from the clinical behavior of LCH.

Widespread secondary macrophage activation in LCH can be diagnostically confounding and may contribute to the clinical picture by producing cytopenias. A (weakly hemophagocytic) macrophage/histiocytic response in the bone marrow can lead to an unwarranted diagnosis of direct LCH involvement, and local or systemic macrophage histiocytosis involving marrow, liver, or lymph nodes has led to upstaging of disease. There is also some overlap among the histiocytic disorders, with two or more elements of juvenile xanthogranuloma (JXG), Rosai-Dorfman disease, hemophagocytic syndrome, and Langerhans' cell histiocytosis occurring in the same patient, sometimes even in the same lesion.

A family of clinical disorders that has a biologic spectrum not unlike that of LCH, varying from solitary lesions to systemic and sometimes lethal disease, has the phenotypic and morphologic characteristics of JXG. Lesions are variably xanthomatous; contain Touton-type giant cells; and are FXIIIa⁺, fascin⁺, CD68⁺, CD1a⁻, and usually S100⁻. This is the lesion most commonly confused with LCH, and diagnostic difficulties ensue when clinical presentation occurs in sites other than skin, such as deep soft tissues, brain, meninges, liver, bone, or larynx. The lesions of xanthoma disseminatum and Erdheim-Chester disease have similar phenotype. Although JXG-type lesions usually involute spontaneously, slowly, over years, local and systemic progression is documented and some have been refractory to systemic therapy and lethal.

The most common macrophage-related systemic disorder in young children is primary hemophagocytic lymphohistiocytosis (HLH), which is familial in approximately half of the cases (FHL). A 10q21-22 mutation is now identified in fewer than half of the familial cases. There are few differences between FHL and the hemophagocytic syndromes that occur in association with known genetic defects such as Chediak-Higashi, Griscelli, and Duncan syndromes (XLP); with some hematologic malignancies; and with a variety of infections, notably Epstein-Barr virus. Control of the primary inciting condition often leads to disappearance of the hemophagocytic syndrome, whereas in FHL, the course is relentless. Thus, it is likely that the familial disorder is a macrophage dysregulation caused by defective T-cell negative control rather than a neoplastic proliferation. HLH and FHL can, however, manifest with tissue- or organ-based masses that are morphologically and phenotypically macrophage in nature, CD68⁺, LN5⁺, and S100[±]. The hemophagocytic element entrenched in the name of these conditions is overstated and may be subtle at best. Organ-based lesions of HLH, such as pulmonary or cerebral nodules and lymph node infiltrates, may not have apparent hemophagocytosis. The diagnosis of FHL/HLH is still based on a composite of clinical, laboratory, and morphologic findings, of which marrow involvement is classical but not invariable. Given the right context, the diagnosis can be established with liver or lymph node involvement in the absence of diagnostic bone marrow involvement.

CASE STUDIES OF TRUE HISTIOCYTIC AND DENDRITIC CELL MALIGNANCIES

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Two examples of true histiocytic malignant tumors and two examples of follicular dendritic cell tumors are presented to emphasize diagnostic criteria and problems in differential diagnosis.

True Histiocytic Malignant Tumor

Criteria for the diagnosis of a true histiocytic malignant tumor are the following: (1) histologic features consistent with a histiocytic tumor (*i.e.*, large cells with slightly eccentric round to oval nuclei containing one or more small nucleoli and with abundant eosinophilic cytoplasm); (2) sufficient nuclear atypia to warrant a diagnosis of malignancy; and (3) immunophenotypic reactivities supportive of histiocytic differentiation (CD68 ± lysozyme ± S100) and lack of reactivities suggesting T-cell (CD3, etc.), B-cell (CD20/CD79a, etc.), granulocytic (MPO), Langerhans' cell (CD1a), or follicular dendritic cell (CD21, etc.) differentiation.

Case 1: True histiocytic malignant tumor ("well differentiated"). This example resides at the cytologically bland end of the spectrum that may be seen in these tumors. If phagocytosis of erythrocytes is present, the

findings may simulate a virus- or lymphoma-associated hemophagocytic syndrome. Immunophenotypic and/or molecular studies are useful in identifying Epstein-Barr virus or other viruses as a causative agent and in identifying a T-cell, NK-cell, or rarely B-cell lymphoma. When phagocytosis of erythrocytes is not prominent, immunophenotypic and/or molecular studies may be important in identifying a histiocyte-rich B-cell, T-cell, or anaplastic large cell lymphoma.

Case 2: True histiocytic malignant tumor (“poorly differentiated”). Histiocytic tumors at the malignant end of the cytologic spectrum raise a wide differential diagnosis. B-cell, T-cell, and especially anaplastic large cell lymphomas may on occasion simulate a true histiocytic malignancy. Immunohistochemical stains specific for the B and T lineages as well as CD30 are important in this setting. Epithelial markers are important for excluding a carcinoma that may simulate a histiocytic malignancy. Because CD68 may be expressed by melanomas and sarcomas and S100 is regularly expressed by melanomas and some sarcomas, the expression of an hematolymphoid-specific marker such as CD45/CD45RB, CD45RO, or CD43 may be important in supporting a diagnosis of a true histiocytic malignancy.

Follicular Dendritic Cell Tumor/Sarcoma

Criteria for the diagnosis of a follicular dendritic cell tumor/sarcoma are the following: (1) histologic features consistent with a follicular dendritic cell tumor (*i.e.*, proliferation of large, generally fusiform cells with an oval, central nucleus with a delicate nuclear membrane, finely dispersed chromatin and small but prominent nucleolus arranged in syncytial, fascicular or whorled patterns and with interspersed single or clustered lymphocytes); (2) immunophenotypic reactivities supportive of follicular dendritic cell differentiation (CD21 and/or CD35 and/or CNA.42) and lack of reactivities for epithelial cells (except EMA, which may be expressed), melanocytes (except S100, which may be expressed), and Langerhans’ cells (CD1a); (3) ultrastructural studies may be useful by demonstrating interdigitating villous processes and desmosomes (also demonstrable by staining for desmoplakin).

Case 3: Follicular dendritic cell tumor/sarcoma. Because these tumors share common histologic features with interdigitating dendritic cell tumors, immunophenotypic and/or ultrastructural support for follicular dendritic cell differentiation is required to make the distinction. Although any spindled lesion including rare lymphomas may enter into the differential diagnosis of a follicular dendritic cell tumor/sarcoma, thymomas and nasopharyngeal carcinomas may most closely simulate these neoplasms in the mediastinum or cervical region but can be distinguished by their cytokeratin reactivity. In the abdomen, gastrointestinal stromal tumors may be differentiated by their CD34 reactivity. Inflammatory pseudotumors with a prominent lymphocytic infiltrate will show markers of myofibroblastic differentiation such as smooth muscle actin. CD68, CD20, and rarely lysozyme may be expressed by these tumors, and a few examples have stained for CD45/CD45RB.

Case 4: Follicular dendritic cell tumor/sarcoma simulating nodular lymphocyte predominance Hodgkin’s disease. A rare variant encountered by John K.C. Chan, which manifests in large B-cell nodules, is presented.

HISTIOCYTIC DISORDERS IN THE BONE MARROW: A PATHOLOGIST’S POINT OF VIEW

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The bone marrow is home to several distinctive histiocytic proliferations, both clonal and nonclonal. The clinical course of these disorders does not

necessarily conform to clonality; the most aggressive of them, hemophagocytic syndrome, is reactive rather than neoplastic in nature.

Nonclonal histiocytoses show two types of morphology in the bone marrow: hemophagocytic and storage. Hemophagocytic histiocytes are a normal component of the marrow and are increased in disorders that are characterized by increased hematopoietic cell turnover, such as megaloblastic anemia and hemoglobinopathies. In these settings, the peripheral cell counts remain essentially unaffected and systemic symptoms are absent.

Much more serious is the florid hemophagocytosis seen in infants and in patients with infections, autoimmune disorders, and malignancies, especially T-cell lymphoma. This type of hemophagocytosis constitutes a specific disorder, “hemophagocytic syndrome.” The diagnosis is made not only on the finding of hemophagocytic cells in the bone marrow and other histiocyte-containing sites but also on the presence of clinical signs and symptoms. These include fever, pancytopenia, hyperferritinemia, hypertriglyceridemia, and hypercytokinemia. The diagnosis of hemophagocytic syndrome must be made with great care, as this disorder carries a 50% mortality rate despite aggressive therapy.

Bone marrow histiocytoses that show storage morphology include both hereditary and acquired disorders. Among the most familiar of the genetic disorders are Gaucher disease and Niemann-Pick disease; many others also involve the bone marrow. The so-called “sea-blue histiocyte syndrome” is likely one of the many Niemann-Pick variants.

Acquired storage disorders result from phagocytosis of cell membranes and other lipids from the peripheral blood. Thus, storage histiocytes are found in immune-mediated cytopenias, total parenteral nutrition, hyperlipidemia, overwhelming mycobacterial infection, and other unrelated settings. In both hereditary and acquired disorders, storage histiocytes are seen as sea-blue and foam cells. It follows that a careful clinical history must be obtained before making the diagnosis of a specific storage disorder.

Clonal bone marrow “histiocytoses” consist essentially of only acute myeloid leukemia (AML) and Langerhans’ cell histiocytosis. Of the many types of AML, acute monocytic leukemia typically is the only one cited as a neoplasm of monocytic/histiocytic origin. However, the precise definition of “monocytic” as applied to AML is not entirely clear. In addition, hemophagocytosis is regularly found in nonmonocytic leukemias, such as AML with t(8;16). Thus, the limitation of neoplastic “monocytic/histiocytic” disorders of the marrow to acute monocytic leukemia may be too restrictive.

Although the marrow may be involved in Langerhans’ cell histiocytosis, it is not often the primary site of diagnosis. The disease appears in the marrow as it does in the skin and lymph nodes, as a proliferation of oval to spindled cells with an elongated, grooved nucleus.

Rare histiocytoses have been described elsewhere in the body. Although some involve bone, creating lytic lesions, few have been reported to involve the bone marrow *per se*. These uncommon disorders include sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) and Erdheim-Chester disease, which have rarely been reported in the marrow; and juvenile xanthogranuloma, xanthoma disseminatum, the dendritic cell neoplasms (follicular, interdigitating, and fibroblastic), histiocytic cytophagic panniculitis (a controversial entity), and true histiocytic malignant tumors, which have not been reported in the bone marrow.