CHAPTER

26 Histiocytosis

Histiocytosis constitutes a rare diverse group of disorders which have in common proliferation of immune cells of the dendritic/macrophage system. The normal function of these cells is to present antigens to lymphocytes. Histogenetically, these cells are of bone marrow origin (myeloid or mesenchymal stem cells), and not lymphocytes, hence they deserve a chapter of their own, separate from lymphoma.

The recent accepted terminology of this group is histiocytosis. Previous historical terms include: reticulosis, reticulum cell sarcoma, histiocytic lymphoma and histiocytosis-X. The biologic behavior of these disorders varies considerably, and major developments were made in recent years in their classification, phenotyping and risk assessment. The present chapter reviews these recent advances.

GENERAL CONSIDERATIONS

Histogenesis

Langerhans, dendritic, interdigitating dendritic and plasmacytoid dendritic cells, all arise from myeloid stem cells (Fig 26-1). The ontogenic (developmental) relation of Langerhans cell lineage is presented in (Fig 26-2). Circulating progenitor predendritic cells in blood give rise to Langerhans

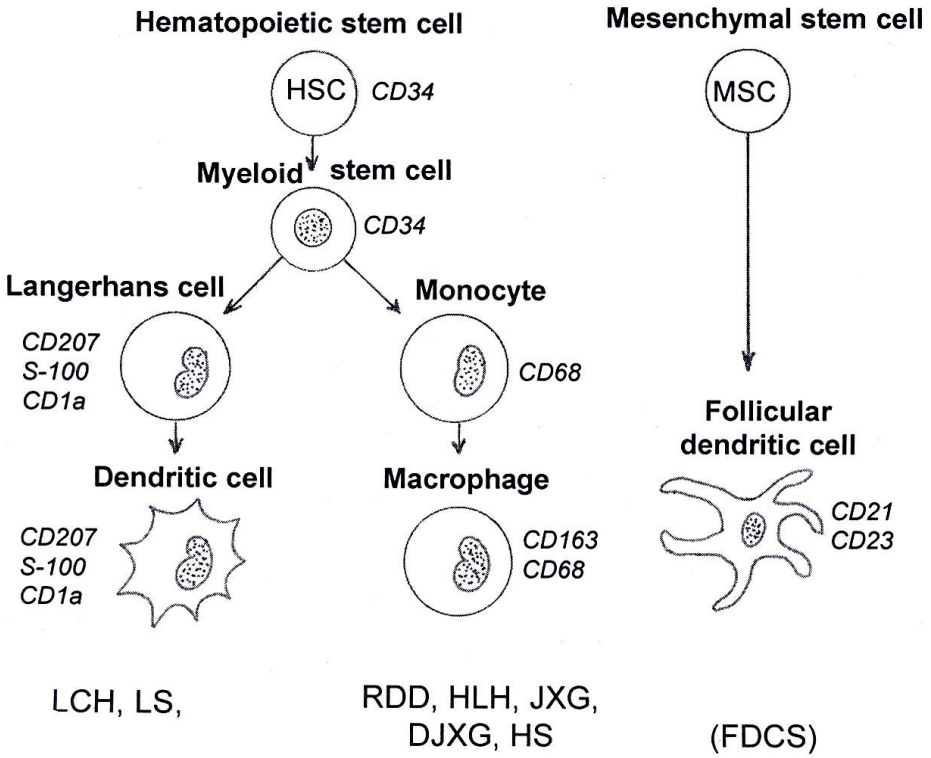

Fig 26-1 *Histogenesis of histiocytic and dendritic cells. Also shown are their immunophenotyping and the diseases derived from them (adapted from Swerdlow et al, 2008). Abbreviations: LCH Langerhans cell histiocytosis, LS Langerhans sarcoma, RDD Rosai-Dorfman disease, HLH hemophagocytic lymphohistiocytosis, JXG Juvenile xanthogranuloma, DJXG Disseminated xanthogranuloma, HS Histiocytic sarcoma and FDCS Follicular dendritic cell sarcoma.*

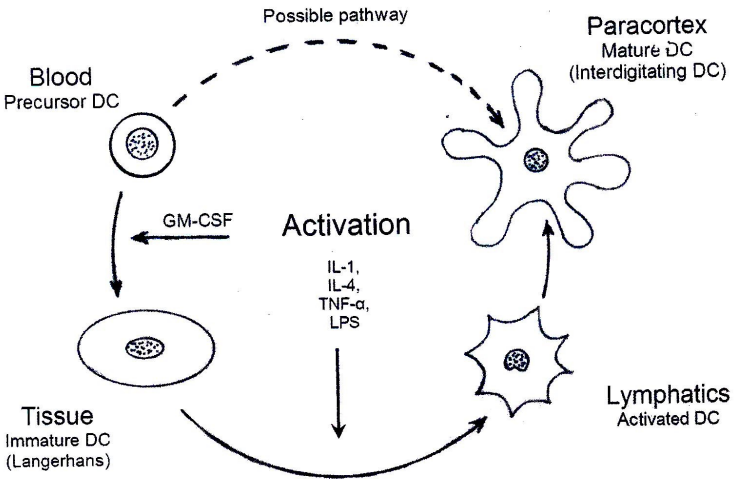

Fig 26-2 *The dendritic cell (DC) cycle. Activation of a precursor DC by granulocyte-monocyte colony stimulating factor (GM-CSF) produced by macrophages and T cells will lead to Langerhans cell. The latter when activated by (LPS) lipopolysaccharide (of bacterial membrane origin) or other cytokines (IL and TNFα) will lead to dendritic cells (adapted from Jaffe et al, 2011).*

cells which upon stimulation (by infection, growth factors or cytokines) will transfer to active dendritic cells with characteristic cytoplasmic processes. Dendritic cells migrate through lymphatics and stay in paracortex of lymph nodes as mature dendritic and interdigitating cells.

Macrophages are phagocytic cells which have a high lysosomal enzyme content and are derived from bone marrow monocytes, which are in turn derived from myeloid stem cells (Fig 26-1). Macrophages may be freely mobile or fixed in tissues Examples of the latter are: tangible body follicular histiocytes, sinusoidal histiocytes in lymph node and spleen, Kupffer cells in liver, alveolar macrophages in the lung, osteoclasts in bone and brain microglia. Dendritic cells and macrophages present antigens to T-helper lymphocytes (CD-4) in the form of peptides and in association with MHC-II molecules (Chapter 8).

Follicular dendritic cell and fibroblastic reticulum cells arise from mesenchymal stem cells (Fig 26-1). The former cells are stationary at germinal centers of lymph nodes and function to present antigens to B-lymphocytes.

Immunohistochemistry

Histiocytic disorders are classified into three main classes according to their phenotype (Table 26-1), namely: (A) Langerhans cell histiocytosis (Langerin (CD 207) a protein product of Birbek granules, S-100 and CDla positive), (B) non-Langerhans histiocytosis including: Histiocytic sarcoma (CD 163 and CD 68 positive) and follicular dendritic cell sarcoma (CD 21 positive) and (C) metatypical histiocytosis which does not fit into one of the above-mentioned classes either due to

Table 26-1 Classification of Histiocytosis

I. Non-neoplastic Histiocytosis
- A. Reactive sinus histiocytosis (SH)
- B. Sinus histiocytosis with massive lymphadeuopathy (SHML). Rosai-Dorfman Syndrome (RDS)
- C. Hemophagocytic lymphohistiocytosis (HLH)
- D. Lipid storage disorders (Nieman-Pick, Gaucher and Tangier syndromes)

II. Neoplastic Histiocytosis

A. Langerhans cell histiocytosis **(LCH)**
1. Single system
2. Multisystem
3. Langerhans sarcoma (LS)

B. Non-Langerhans cell histiocytosis

Benign
1. Xanthoma
2. Juvenile xanthogranuloma (JXG)
3. Disseminated juvenile xanthogranuloma (DJXG)
4. Erdheim-Chester disease (ECD)

Malignant
1. Monocytic leukemia (ML)
2. Histiocytic sarcoma (HS)
3. Follicular dendritic cell sarcoma (FDCS)

C. Metatypical histiocytosis
1. Interdigitating dendritic cell sarcoma (IDC)
2. ALK positive histiocytosis
3. Fibroblastic reticular cell tumor (FRCT)
4. Indeterminate dendritic cell tumor

(Jaffe et al, 2011)

lack of expression of a specific histiocytic marker, co-expression of markers of both classes or aberrant expression of non-histiocytic markers (e.g. cytokeratin, actin or desmin). In general, langerin (CD 207) and CD 163 are more specific than other markers in identifying the immunophenotypic class of a given histiocytic tumor.

Classification

A recent classification of histiocytic proliferations and tumors is presented in (Table 26 -1) based upon their clonality, biologic behavior and phenotyping (Jaffe et al, 2011). This system separates these disorders into two main groups: (I) a non-neoplastic class (which is polyclonal hyperplastic lesions) and (II) a neoplastic class (which is monoclonal) and includes: Langerhans type, non-Langerhans type and metatypical histiocytosis. Langerhans cell disease was classified in the past as a hyperplastic disorder, but at present it is considered a neoplastic disease in view of its monoclonality and response to chemotherapy.

SPECIAL CONSIDERATION
NON-NEOPLASTIC HISTIOCYTOSIS

Reactive Sinus Histiocytosis (SH)

This refers to hyperplasia of phagocytic histiocytes in sinuses of lymph nodes draining an inflammatory lesion or a tumor (P 26-1). It may also be observed in sinuses of the red pulp of spleen in hemolytic disorders or hypersplenism.

Sinus Histiocytosis with Massive Lymphadenopathy (SHML)/Rosai-Dorfman Disease (RDD)

Classically, it presents as bilateral, painless, massive, generalized lymphadenopathy associated with fever and elevated ESR (Patterson et al, 2006). It is most common in children. About 25% of patients have extranodal involvement (mainly skin, orbit and upper respiratory tract). The etiology is obscure, but viral infection was suspectted. In the majority of patients, the disease undergoes spontaneous regression, but few patients die as a result of superimposed complications.

Histologically, lymph node sinuses are mainly affected and histiocytes have abundant cytoplasm rich in lipid. The diagnostic feature is the presence of intact lymphocytes and plasma cells in cytoplasm within vacuoles which protect them from phagocytosis (P 26-3). This phenomenon (emperipolesis) refers to the ability of some cells to traverse the cell membrane of another cell and remain undamaged in cytoplasm. Immunophenotype is characterized by positivity to CD68 and S-100 (but negative for CD1a in 90% of cases).

Hemophagocytic Lymphohistiocytosis (HLH)

Hemophagocytic disorders are due to uncontrolled macrophage activity mediated through T-helper lymphocyte action resulting in phagocytosis of blood cells. HLH is categorized into two main forms (Table 26-3), namely: primary (familial) and

Table 26-2 Immunophenotyping of Malignant Histiocytic Tumors

Marker	Langerhans	Non-Langerhans		Metatypical	
	LCH, LS	HS	FDCS	IDC	FRCT
S-100	+	-	-	+	+
CD1a	+	-	-	-	+
CD-207 (Langerin)	+	-	-	-	-
CD 68	-	+	-	±	+
CD 163	-	+	-	-	-
CD 21	-	-	+	-	-

Aberrant expression of cytokeratin, actin and desmin CD-207 (Langerin) and CD163 are more specific than other markers for identifying Langerhans and non-Langerhans tumors respectively.
Abbreviations: LCH Langerhans cell histiocytosis, LS Langerhans sarcoma, HS histiocytic sarcoma, FDCS Follicular dendritic cell sarcoma, IDC Interdigitating dendritic cell histiocytosis, FRCT Fibroblastic reticular cell tumor

Table 26-3 Differential Diagnosis of Hemophagocytic Lymphangiohistiocytosis (HLH)

	Primary (Familial)	Secondary (Acquired)
Age	Infancy	Adult
Familial affection	Present	Absent
Perforin mutation	Present	Absent
NK cell number	Normal	Reduced
Immunodeficiency	Absent	Present
Predisposing disease	None	Infections, lymphoma autoimmunity
Lab tests	Normal	Raised ESR
Course	Progressive	Remissions
Fatality	50 - 100%	20%

The diagnosis of HLH is established by either genetic criteria and/or 5 of the other 8 clinial and laboratory criteria (Orkin et al, 2009)

Table 26-4 The Revised Diagnostic Criteria of Hemophegocytic Lymphohistiocytosis (HLH)

I. **Molecular Genetic Criteria**
- Mutation of PRF (Perforin) and related genes

II. **Clinical and Laboratory Criteria**
- Fever
- Splenomegaly
- Cytopenia
- Hypertriglyceridemia and/or Hypofibrinogenemia
- Hemophagocytosis by pathology
- Low or absent NK cell cytotoxicity
- Hyperferritinemia
- Elevated soluble CD25

(Histiocyte Society, 2006)

secondary (acquired). Both share a similar histologic picture (P 26-3) and clinical presentation of a systemic disease (fever, rash, splenomegaly and weight loss), but, differ in pathogenesis and prognosis. The familial type is due to mutation of perforin gene (PRF1) and other related genes (UNC 13 D and syntaxin genes). Perforin plays a key role in cell-mediated cytotoxicity. It is secreted from cytotoxic T-cells and NK cells, induces pore formation in cell membrane of target cells and hence allowing granzyme to enter and triggers apoptosis. Accordingly, loss of perforin will result in increase of histiocyte survival. Primary HLH affects infants and is rapidly fatal without immune -modulating therapy and blood transfusions. Conversely, secondary HLH is more common, observed in patients with immunosuppression, may be associated with viral infection (EBV) and prognosis is more favorable. Diagnostic criteria of HLH are presented in (Table 26-4).

Lipid Storage Disorders

Lysosomes, which are rich in macrophages, contain a battery of enzymes which catalyze the breakdown of a variety of complex macromolecules (including lipids). Genetic mutations with loss of this enzyme function will lead to the accumulation of the insoluble partly degraded metabolites within the lysosomes. Three lipid storage syndromes are described according to the stored material (Table 26-5). In Gaucher disease, the accumulated metabolites are observed in macrophages in bone marrow, lymph nodes and spleen. Contrary to other lipid-storage disorders, the cytoplasmic material is not vacuolated but fibrillary in appearance (P 26-4).

Langerhans cell Histiocytosis (LCH)

This refers to a localized or disseminated monoclonal proliferation of Langerhans cells. For confirmation of diagnosis, the histiocytic cells must be positive for langerin (CD 207) or Birbek granules demonstrated by electron microscopy. The etiology is obscure, but there is association with hematologic malignancies. The tumors affect mainly children (Peak age 1-3 years).

In the past, three different syndromes were described, namely: (1) Eosinophilic granuloma (75%), a benign form affecting children and young adults, (2) Hand-Schuller-Christian disease (15%) a chronic disorder affecting children with frequent CNS involvement (diabetes insipidus and neurodegenerative symptoms), and (3) Letterer-Siwe disease (10%), an aggressive form affecting infants. This classification has limited value to guide therapy. A recent classification based on stage of disease into single system (P 26-5) and multisystem (P 26-6) is most useful to guide

Table 26-5 Lipid Storage Disorders

Syndrome	Stored material
Niemann-Pick	Sphingomyelin And cholesterol
Gaucher	Glucocerebrosides
Tangier	Sterols

Table 26-6 Classification of Langerhans cell Histiocytosis According to the Extent of Disease

	Single System [a]	Multisystem
Age	childhood	Infancy
Site	Bone, lymph node	Bone, skin, organs
Blood	Normal	Cytopenia Elevated ESR
Treatment	Observation	Vinblastine, Steroids
Prognosis	Excellent 99% survival	Poor, fatal in 25-66% [b]

(a) May be unifocal or multifocal in the same location. (b) Fatality is high (65%) if risk sites are affected (bone marrow, liver or lung).

therapy and predict prognosis (Table 26-6). Moreover, in the multisystem class, involvement of high risk sites (Bone marrow, liver or lung) is associated with serious life threatening course of the disease (Orkin et al, 2009).

Histopathology: The diagnostic feature of LCH is Langerhans cells, an oval non-dendritic cell (10-26 microns) with abundant eosinophilic cytoplasm, eccentric folded and grooved nuclei (P26-7 and P26-8). The cells are langerin (CD 207), S-100, CD1a positive. Birbeck granules are evident by electron microscopic study (P 26-9). LCH lacks cytologic atypia and there is often associated eosinophils and lymphocytes. Macrophage activation may occur in certain sites (bone marrow and spleen) and obscure the histologic picture causing misdiagnosis.

Differential diagnosis: In lymph node biopsies, LCH must be distinguished from dermatopathic lymphadenitis and necrotizing lymphadenitis. Dermatopathic lymphadenitis is paracortical in location, macrophages contain melanin pigment and lack eosinophil cell infiltrate. Necrotizing lymphadenitis is characterized by geographic areas of necrosis and apoptosis. In bone biopsies, LCH must be distinguished from chronic osteomyelitis and Ewing sarcoma, especially cases complicated by fractures since the lesion will be rich in histiocytes. Osteomyelitis lesions are rich in plasma cells, neutrophils and fibrocytes. In Ewing sarcoma, malignant round cell (CD 99 positive) with scanty cytoplasm will be evident.

Langerhans Sarcoma (LS)

This rare malignant tumor is confined to adults and fatal in 50% of patients. It presents in 3 clinical settings : (1) Malignancy on top of LCH, (2) Malignancy complicating T-cell lymphoblastic leukemia, and (3) Malignant from the start (de-novo or primary type). Histologically, the histiocytic cells show anaplastic features (pleomorphic nuclei, prominent nucleoli and active mitosis), but retain LCH phenotype (positive langerin).

BENIGN NON-LANGERHANS HISTIOCYTOSIS

Xanthoma

This is observed in old patients with disorders of lipid metabolism (e.g. hypercholesterolemia) and the skin of eye lid is commonly affected. Histologically, lipid containing macrophages with foamy cytoplasm are evident (P 26-10).

Juvenile Xanthogranuloma (JXG)

Juvenile xanthogranuloma is a benign non-Langerhans histiocytosis involving mainly the skin of infants and children (Patterson et al, 2006). The tumor affects most often the head and neck region, presenting as reddish papule (0.5-1 cm). Histologically, the lesion is dermal in location, composed of foamy macrophages, touton giant cells (with circular arrangement of nuclei). Lymphocytes, eosinophils and mast cells (P 26-11). The histiocytes in the tumor are positive for CD 163, and CD 68, but negative for S-100 and langerin.

Xanthoma disseminatum and *Erdheim-Chester* disease may represent adult variants of JXG (Jaffe

et al, 2012). Xanthoma disseminatum presents as multiple cutaneous tumors. Erdheim-Chester disease (ECD) involves the bone, lung and CNS (polyostotic sclerosing histiocytosis). The immunophenotype of ECD is metatypical (Positive S-100, but, negative langerin and CD1a).

MALIGNANT NON-LANGERHANS HISTIOCYTOSIS

Monocytic leukemia

Monocytic leukemia affects young adults and is always acute in presentation, constituting only 5% of acute myeloid leukemia. By definition, blasts should constitute >20% of cells in blood or bone marrow, and 80% or more of the leukemic cells are of monocytic lineage (monoblasts and monocytes). A minor neutrophil component (<20%) may be present, but if this exceeds 20% the case is termed acute myelomonocytic leukemia (5-10% of acute myeloid leukemia). Monocytic leukemia exhibit a non-Langerhans phenotype (CD163 and CD68 positivity).

Histiocytic Sarcoma (HS)

It is mainly a disease of adults and affects lymphoid tissue, constituting only 0.5-1% of lymphomas. The term histiocytic sarcoma is preferable than histiocytic lymphoma because the tumor is not derived from lymphocytes. Histologically, it is characterized by sinusoidal pattern, abundant cytoplasm which may show hemophagocytosis, eccentric nuclei, prominent nucleoli and multinucleation (P 26-12). The immunophenotype is CD163, CD 68 and lysozyme positivity.

Differential diagnosis: HS must be distinguished from: anaplastic large cell NHL (CD 30 and ALK positive and CD 163 negative) and myeloid sarcoma (myeloperoxidase and CD34 positivity).

Follicular Dendritic cell sarcoma (FDCS)

FDCS affect mainly adults, 70% are nodal and 30% extranodal presentation. It was formerly named reticulum cell sarcoma. About 15% are associated with Castleman disease hyaline vascular type. Histologically, it is composed of bundles of spindle cells with storiform or whorled pattern and may be associated with lymphocytes and fibrosis (P 26-13). Positivity to CD 21 is confirmatory. Generally, FDCS is of lower grade compared to lymphomas.

Differential diagnosis: FDCS must be distinguished from interdigitating dendritic cell sarcoma (CD 21 negative and S-100 positive), thymoma (cytokeratin positive) and melanoma (Melan A positive).

METATYPICAL HISTIOCYTOSIS

Interdigitating Dendritic cell Histiocytosis (IDC)

Histologically, it is similar to follicular dendritic cell histiocytosis (P 26-14) but the immunophenotype is different (Negative CD 21 and CD 163, but positive S-100), shows more prominent dendritic processes and more aggressive clinical course

ALK Positive Histiocytosis

This is an aggressive tumor of infants, immunoreactive for ALK, CD 68 and S-100.

Fibroblastic Reticular Cell Tumor (FRCT)

It affects lymph nodes or soft tissue, shows a spindle cell and collagen morphology (positivity to S-100, Actin and cytokeratin, but negative to other histiocytic markers). Electron microscopy shows prominent dendritic processes and desmosomes and absent Birbek granules .

Indeterminate Dendritic cell Tumor

It presents as a cutaneous lesion, rounded cell morphology (predendritic cell origin) and complex immunophenotyping (Positivity to S-100 and CD1a, but Langerin negative and CD68 may be positive).

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