

Pathologic Diagnosis of the Histiocytic Disorders of Childhood

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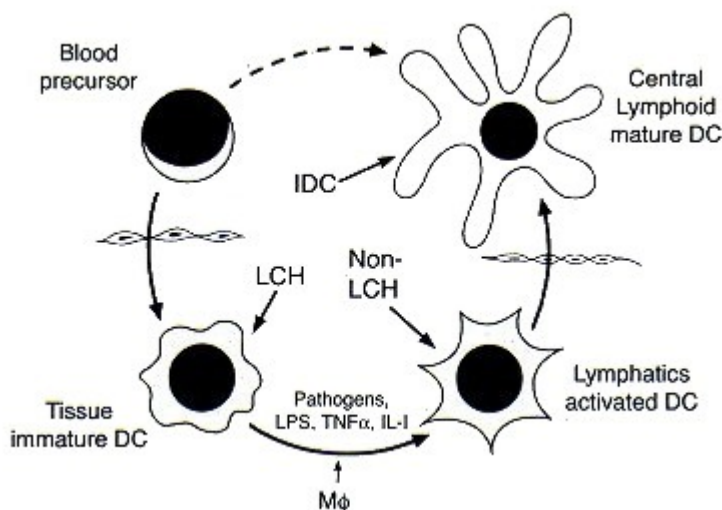
Histopathology, the diagnosis of disorders from the examination of tissues, and cytopathology, diagnosis made from cells, remain the mainstay of the rare and unusual conditions known as the childhood histiocytoses. The basic principle is that each of the histiocytic disorders is defined by the unique cells that constitute the different diseases. The Histiocyte Society that met for the first time in 1985 set itself that task of defining the individual disorders and laying out diagnostic criteria that were reproducible. There is now a "contemporary classification of histiocytic disorders"¹ and a set of "diagnostic guidelines" for hemophagocytic histiocytosis² that are broadly applicable to the range of proliferation disorders of histiocytes. This review deals with diagnostic criteria used by pathologists to define the categories listed in the classification.¹

Histiocyte Differentiation

There are two broad lines of cell differentiation that are included under the title of "histiocytes," the dendritic cells and those of the monocyte-macrophage series, though the two share at least some common origin and may not be as clearly separable as the classification implies. There is evidence that cytokines can modulate the cells to behave as one or the other line.

The current classification divides the disorders into those of varied (and often unpredictable) biological behavior and those that are frankly malignant. Each of these is subdivided into diseases of the dendritic cells and macrophage-related conditions.

The specific diagnosis is achieved by identifying the constituent cells making up the majority of a given lesion and determining, using microscopy and immunophenotyping, exactly which cell predominates. The type of cell can be matched to their counterpart in the normal life cycle of the corresponding normal histiocyte, as shown in figure 1.



Thus, immature Langerhans-type dendritic cells are the sine qua non of Langerhans cell disease, and there are non-Langerhans dendritic cell lesions that can be more or less mature than the Langerhans cells. Dermal and interstitial dendritic cells are responsible for juvenile xanthogranulomas and xanthoma

disseminatum. Macrophages are the predominant cell in the hemophagocytic syndromes, even though it is now clear that they are reacting to defective T-cell signals.

Diagnostic Methods

Histiocytic disorders are rare and often unsuspected, so it is unusual to have fresh tissues available for flow cytometric analysis. As it is, there are few antibodies available for flow cytometric characterization of dendritic cells. Immunohistochemistry on fixed tissues is the standard for diagnosis. By using a limited panel of antibodies that recognize dendritic cells and macrophages at various stages of maturation, (Table 1) the various lesions can be categorized.

Table 1

	Immature DC	Activated DC	Mature DC
CD1a	hi	lo-absent	0
Langerin	hi	lo-absent	0
HLA-DR (LN3)	paranuclear	paranuclear + membrane	membrane hi
Fascin CD68 (KP-1/PGM-1)	0-lo paranuclear	lo-mod cytoplasm fine granular	hi cytoplasm
Rel B CD83 DC Lamp	cytoplasm 0 0	cytoplasm 0 0	nuclear hi hi

Panels of antibodies are required because there are no markers unique to these cells. Table 2 lists the various cell types, the markers that identify them, and the disorders that they characterize. Unfortunately for those who have to make the diagnosis, diseases have a natural history so that cell types may change their appearance and phenotype with time, with maturation or with treatment. Lesions may involute or scar, and the host can launch an inflammatory or immune reaction that can obscure the nature of the lesion. It is often the synthesis of clinical, imaging and histopathologic features that establishes a firm diagnosis.

Complicating Factors

There are a number of complicating factors in the diagnosis and characterization of the histiocytic disorders, even the most common of them, Langerhans cell histiocytosis (LCH). Most of the conditions are rare, and there are few pathologists who feel comfortable making the diagnosis of the entire range of lesions. There are limited numbers of markers applicable to the lesions in fixed tissues, and even those are not unique. There is biological overlap that is often confounding. For example, juvenile xanthogranulomas can occur in children with LCH, and it is not unusual to find an element of macrophage activation in the organs of children who have localized or systemic LCH, especially in the liver and marrow.^{3,4} This secondary histiocytosis can lead to an erroneous assumption that the organs are involved by LCH and lead to over-staging and possible over-treatment.

Since disorders such as systemic juvenile xanthogranuloma and non-Langerhans cell histiocytosis are so rare, there is little reliable information on their natural history or preferred treatment. Worst of all is the rampant confusion and disorder in the literature, replete as it is with single-case reports that lack meaningful followup and the use of idiosyncratic terminology.

The hope is that through the efforts of the Histiocyte Society, enough of these lesions will become available for study and categorization with careful clinical monitoring.

Table 2

Histiocytic and Dendritic Cells and Their Disorders		
Histiocytes	Phenotype	Disorder
Langerhans cell	CD1a, Langerin, S100, Birbeck granules	Langerhans cell histiocytosis
Indeterminate cell	CD1a, S100, no Birbeck granules	Dendritic cell histiocytoma/indeterminate cell type
Activated dendritic cell	HLA-II membrane, fascin-mod, CD68, S100	Dendritic cell histiocytoma/activated cell type
Interdigitating dendritic cell	Fascin hi, S100 hi, CD83, DC-LAMP	Dendritic cell hyperplasia and dendritic cell histiocytoma, interdigitating cell type
Dermal and interstitial dendrocytes	Factor XIIIa, fascin, CD68	Xanthogranuloma family, xanthoma disseminatum
Follicular dendritic cell	CD21, DC35, Ki-M4, S100+/-, fascin	Dendritic cell histiocytoma/follicular dendritic cell type
Putative sinus dendritic cell	Ki-M9, fascin, CD68, S100	Possibly Rosai-Dorfman disease
Macrophage	CD68, LN5	Hemophagocytic disorders

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