

## ***Selective Quotations from Reading on Pathology of LCH & JXG***

### **General**

***Blood, Vol. 94 No. 12 (December 15), 1999: pp. 4195-4201***

Lesions of LCH are polymorphous, featuring a monoclonal population of CD1a+ histiocytes with a phenotype akin to that of cells of the antigen-presenting Langerhans cell family. T cells, macrophages, and eosinophils are variably present. The key histiocyte of LCH and its normal counterpart, the Langerhans cell, express CD1a and S-100 and contain Birbeck subcellular organelles.<sup>3</sup> In contrast to normal Langerhans cells, the principal histiocytes of LCH (LCH cells) are actively proliferating, have a round rather than dendritic shape, and express several contrasting antigenic markers.

***Cameron K Tebbi, MD, Medical Director, Department of Pediatric Hematology-Oncology, Tampa Children's Hospital***

The following outline adapted from the Writing Group of the Histiocyte Society (Chu, 1987) describes confidence levels for the diagnosis of class I Langerhans cell histiocytosis: Presumptive diagnosis - Light morphologic characteristics Designated diagnosis - Light morphologic features plus two or more supplemental positive stains for Adenosinetriphosphates, S-100 protein, a-D-Mannosidase, Peanut lectin Definitive diagnosis - Light morphologic characteristics plus Birbeck granules in the lesional cell with electron microscopy and/or staining positive for CD1a antigen (T6) on the lesional cell

***Ronald Jaffe, The Histiocytoses, Diagnostic Pediatric Hematology***

The gold standard of diagnosis has been the identification of the ultrastructural Birbeck or Langerhans cell granule, because none of the other tissue or cell markers is unique to LCH. However, at the practical level, the demonstration of CD1a molecules on the surface of cells that appear to be LCH cells in the appropriate clinical setting is sufficient to consolidate a diagnosis.

***Ronald Jaffe, The Histiocytoses, Diagnostic Pediatric Hematology***

It is not uncommon for a bone lesion to be identified in a child in which the differential diagnosis on imaging includes LCH versus osteomyelitis, infectious or chronic relapsing forms. The difficulty arises when the lesion is sampled and does not contain the sheets of LCH cells so typical of the usual lesion. Evolving LCH lesions are filled in by fibrosis and inflammatory cells as the pathognomonic LCH cells disappear.

***Philip A. Pizzo, David G. Poplack, Principles and Practice of Pediatric Oncology: Chpt 26, "Histiocytoses" By Stephan Ladisch and Elaine S. Jaffe***

"The cells of LCH demonstrate the phenotypic characteristics of normal Langerhans' cells, including S100 positively, CD1a(OKT6) expression, and Birbeck granules. However, in contrast to normal Langerhans' cells, the cells of LCH also express leukocyte adhesion molecules, such as CD11 and CD14, typically expressed in greater density on phagocytic histiocytes.....

.....The key pathologic finding in LCH is the presence of Birbeck granules, detected by electron microscopy, in cells of the lesions."

***Arch Pediatr Adolesc Med/Vol 152, Jan 1998***

By immunohistochemistry, LCH characteristically comprises HLA-DR+, CD1a+, S100+, CD15+, CD30-, and CD11c+ proteins. Many of these proteins are found in other cells, such as S100 protein in melanocytes, neural cells, chondrocytes; however, the presence of Birbeck granules detected by electron microscopy or expression of CD1a by immunohistochemistry is considered diagnostic of LCH. Expression of CD1a requires frozen sections or fresh cytologic preparations; however, a new monoclonal antibody, MAb 010, recognizes an epitope of CD1a in paraffin-embedded tissue and is more specific than S100 protein in routinely fixed tissue for the diagnosis of LCH.

***Lancet, 1987; I:208-9***

Under the recommendation of the Writing Group of the Histiocyte Society, a definitive diagnosis of LCH can only be rendered when either there is demonstration of Birbeck granules on electronmicroscopic study or there is a demonstration of CD1a expression with appropriate histological settings.

## ***Selective Quotations from Reading on Pathology of LCH & JXG***

### ***Journal of Cutaneous Pathology 2001;28(10 531-537 abstract quote***

"Results: Spindling histiocytes were positive for S100 and CD1a. The monocytic/macrophage marker, CD68, and the dendritic cell marker, CD21, were negative. Electron microscopy failed to reveal Birbeck granules.

Conclusions: Relatively few reports of indeterminate cell histiocytosis exist, some of which include discussion of potential overlaps with the non-X histiocytoses. Although the presence of prominent spindling in our case expanded the differential to include non-histiocytic disorders, the identified histiocytes unequivocally fulfilled the criteria of S-100 and CD1a positivity without demonstrable Birbeck granules."

### ***Histopathology 200 Mar; 36(3):229-31 Abstract quote***

Conclusions: CD101 is the new phenotypic marker that might be useful in combination with other markers for the diagnosis of LCH. However, as the anti-CD101 antibody works only in frozen sections, its value is limited compared to anti-CD1a antibody.

### ***Ultrastruct Pathol 1982 Apr-Jun;3(2):137-42 Abstract quote***

Our data suggest that electron microscopy, even when applied to the study of suboptimally preserved material, is a highly sensitive technique for confirming a diagnosis of histiocytosis X.

### ***J Pathol 1997 Mar; 181(3):301-4 Abstract Quote***

This study shows that dissemination and poor prognosis are associated with lack of E-Cadherin expression in LCH cells. Aggressive clinical evolution of LCH may therefore be related to the loss of functions mediated by E-Cadherin.

### ***Klin Paditr 2000 Jul-Agu;212(4): 139-44 Abstract quote***

Methods: all patients had morphologically confirmed diagnosis, which was additionally verified through demonstration of CD1a antigen, presence of Birbeck granules or central pathologic review

### ***Source?***

"Accumulation of Langerhans cells is the central histopathological feature of LCH. Two unique morphologic features facilitate definitive identification of Langerhans cells. The first is the presence of Birbeck granules, which appear as pentalaminar (five-layered), rod-shaped intracellular structures when visualized by electron microscopy. The second characteristic is the strong presence of the CD1a antigen on the cell surface, a feature not observed in other cells of histiocytic origin."

### ***Source?***

In reference to adult pulmonary LCH, "Immunohistochemical studies are useful in recognizing Langerhans cells, which stain for the S-100 protein, CD1a, and HLA-DR. Langerhans cells may be identified in several pathologic pulmonary processes, and hence the mere presence of Langerhans cells is not diagnostic of pulmonary LCH. Histologic diagnosis of pulmonary LCH in adults rests on the identification of typical lung lesions, coupled with reliable demonstration of increased numbers of Langerhans cells. In experienced hands, this may be achieved by examining routine tissue specimens stained with hematoxylin and eosin."

### ***Source?***

"...epidermal Langerhans cells unexpectedly react positively with a murine monoclonal antibody, OKT6, which was developed to recognize a glycoprotein antigen, clustered as CD1a and normally present on the surface of cortical thymocytes... and this marked a crucial step in the knowledge of Langerhans cells. The ease of the staining process and the narrow specificity of the antibody made it a useful routine procedure to identify isolated CD1a+ cells in pathologic material, tissue culture, and cell suspension, particularly in bronchoalveolar lavage."

## ***Selective Quotations from Reading on Pathology of LCH & JXG***

### ***Source?***

"In 1961, however, a specific structure in the cytoplasm of these cells was detected by Birbeck and coworkers with electron microscopy. These Birbeck granules from then on served as a distinct recognition marker and became a morphologic hallmark."

### **Juvenile Xanthogranuloma**

***European School of Oncology -www.cancerworld.org/progetti/cancerworld/start/pagine/.....***

JXG and LCH can occur in the same patient, suggesting that the pathogenesis of the two conditions may have a common element.

### ***Brain Pathology Case of the Month - September 2000***

Whenever JXG or similar lesions of central nervous system are diagnosed, especially in children and young adults, the LCH should be excluded by electron microscopy. Thoroughly screening of the skin is necessary, since cutaneous lesions often, though not always, precede or accompany the deep lesions.

### **Central Nervous System**

#### ***Central Nervous System Disease in LCH - Nicole Grois, M.D.***

The extraparenchymal lesions (type III) revealed fibroxanthomatous changes also without Langerhans cell phenotype, but some findings were similar to the histology of juvenile xanthogranuloma. These lesions appear like "burnt-out" lesions that lost the classical histology of LCH.

#### ***Ronald Jaffe, The Histiocytoses, Diagnostic Pediatric Hematology,***

Brain involvement is another site where LCH may be difficult to document. LCH has been seen in the hypothalamic-pituitary axis, the choroid plexus, and the meninges. There are instances in which children who have active or even inactive LCH develop cerebellar signs and progressive disease. Repeated biopsy of these sites in some patients has failed to reveal LCH cells, even in lesions documented to be of recent onset by magnetic resonance imaging. This leads to the suggestion that the cerebellar disease may be a paraneoplastic phenomenon and that biopsy is not appropriate.

#### ***Dr McClain***

Brain biopsies are difficult to interpret, Langerhans cells may not be present, cells look like fat macrophage. Recommend Jaffe for Pathology

#### ***Philip A. Pizzo, David G. Poplack, Principles and Practice of Pediatric Oncology: Chpt 26, "Histiocytoses" By Stephan Ladisch and Elaine S. Jaffe***

Curiously, however, the cytologic atypia and particularly the Birbeck granules found by electron microscopy usually are not present in brain or liver tissue, even when these organs are clinically involved in the disease process. Therefore, the lesions in these organ systems may possibly result from a different pathogenetic process.