22 Langerhans Cell Histiocytosis

KENNETH L. MCCLAIN, JOHN J. HUTTER, and J. ROBERT CASSADY

22.1 Introduction

A panel of experts representing the Histiocyte Society has suggested that the original terminology for the various syndromes in the “histiocytosis X” category (eosinophilic granuloma, Letterer-Siwe disease, and Hand-Christian-Schiller syndrome) be discarded and replaced by the term Langerhans cell histiocytosis (LCH) (CHU et al. 1987). This is because the proliferative cell which causes these entities is known to be the Langerhans cell.

This chapter will deal only with the Langerhans cell histiocyte diseases. The benign but aggressive non-Langerhans cell histiocytoses should not be treated with radiation therapy. Malignant histiocytosis is rarer than the LCH syndromes in children and will not be covered here.

22.2 Etiology and Incidence of LCH

There is no known etiology of LCH. One group of investigators has suggested the possibility of a transmissible (viral?) agent (ATHANASIU et al. 1970; NASTAC et al. 1970). Phenol extracts of tissue from bone lesions of LCH patients were injected into mice. Cell suspensions were made from the lungs of the mice and assayed for cytopathic effect on primary human embryo cultures. The presence of syncytia and nuclear changes were taken as evidence of a transmissible agent. On the basis of immunofluorescence studies it was claimed that the cytopathic effect did not result from mouse antigens or mouse viruses. The sera of eosinophilic granuloma or leukemia patients reacted with the extracts of the original eosinophilic granulomas. Since then no specific studies have been published to further elucidate these findings.

A genetic propensity for LCH has not been definitively shown. However, there are several reports in the literature of familial occurrences (SCHOECK et al. 1963; MILLER 1966; KATZ et al. 1991). The earlier reports relied on the histologic tools and criteria of the era, so there could be some doubt as to the diagnoses. However, many of these earlier cases seem to be “classical cases,” as do monozygotic twins with biopsy identification of Birbeck granules (KATZ et al. 1991). If one is to believe the clinical diagnoses, there are at least ten sibships with what was called Letterer-Siwe disease. The caveats stated by KATZ and co-workers in relation to confusion with the non-Langerhans cell histiocytoses are appropriate. However, known HLA type propensities in LCH patients and the identified immunologic abnormalities make familial cases very likely.

It was reported that 23% of LCH patients had major anomalies, including malformations of the central nervous system and renal, vertebral, genitourinary, and several other categories of
malformations, compared to 13% of patients with bone tumors or 15% of a control group.

Although LCH may appear at all ages from birth through adulthood, over half will be diagnosed between the ages of 1 and 15 years (BERRY et al. 1986). In a recent study from Denmark the incidence rate of LCH was reported as 5.4/million (CARSTENSON and ORNVOLD 1991). By comparison, AUSTIN et al. (1988) reported incidences per million children of 47.8 for all acute leukemias, 5.6 for acute nonlymphocytic leukemia, 6.5 for Hodgkin’s disease and 7.9 for Wilms’ tumor (AUSTIN et al. 1988). It has been estimated that approximately 1200 new cases of LCH are seen annually in the United States (LAVIN and OSBAND 1987).

22.3 Pathology and Biology

The abnormal cell in LCH is a bone marrow-derived member of the dendritic histiocytes, also called the Langerhans cell, which contains characteristic five-layered Birbeck granules seen by electron microscopy (EM) (FAVARA 1981) (Fig. 22.1). In skin lesions many cells have these granules, but in other organs the infiltration is often by histiocytes of bone marrow origin which do not contain Birbeck granules. Langerhans cells also stain with monoclonal antibodies to the CD1a (T6) epitope of lymphocytes (MURPHY et al. 1981). The major problem with this marker is the need for fresh- or snap-frozen tissue. Two other markers for the Langerhans cells are peanut agglutinin (PNA) and S-100, which can be used with paraffin-embedded material (McCLELLAND and CHU 1988). PNA produces dense cell surface and paranuclear staining of the LCH cells. Although PNA staining also occurs in Reed-Sternberg cells of Hodgkin’s lymphoma and interdigitating reticulum cells of normal lymph nodes, it is very useful in differentiating non-Langerhans cell histiocytes, which are negative. The S-100 stain is almost as useful as PNA and suffers only from marking normal Langerhans cells and some cases of malignant histiocytosis. Most importantly, the histiocytes found in the non-Langerhans cells histiocytes (virus-associated hemophagocytic syndrome or familial erythrophagocytic lymphohistiocytosis and juvenile xanthogranuloma) are negative.

It is important to use EM and S-100 or PNA staining on suspected LCH specimens because of the variability of results. In a study by YE et al. (1990) on 27 cases of LCH, the S-100 was reactive in 88.5% and PNA in 75%, while EM was positive for Birbeck granules in 47% of cases. Of the negative cases on EM, four were from bone lesions, five from lymph nodes, and one from an ear canal scraping. New reagents are being tried to further aid diagnostic assessments. LUKSCH et al. (1989) used a novel antibody KP1 (CD28) which reacts with LCH cells but not with normal Langerhans cells. It was positive in 18 of 22 cases. Other antibodies used included: anti-CD45 (lymphocyte cell adhesion) (3/22 positive), PNA (21/21 positive), S-100 (21/21 positive), HLA-DR (16/22 positive) and CD30 (Ki I) (0/22 positive). Most experts agree that to establish the diagnosis of LCH, identification by EM of Birbeck granules or staining of Langerhans cells with one of the two special stains or the CD1a marker is necessary.

Histologically the proliferation of LCH cells in solitary bone lesions (formerly eosinophilic granuloma) reveals Langerhans cells with eosinophils, neu-

Fig. 22.1. Electron micrograph of a Langerhans cell from a lymph node showing the diagnostic pentamellar Birbeck granule. (Courtesy of Hal Hawkins, MD, PhD, Texas Children’s Hospital)