

CONTENTS

Preface	xv
R. Maarten Egeler and Giulio J. D'Angio	
Langerhans Cell Histiocytosis: Historical Perspectives	213
Fritz Lampert	
The names and historical events that played a role in the discovery of the Langerhans cell, the identification and definition of Langerhans cell histiocytosis, and the progress of disease management are provided in a short historical review.	
Nosology and Pathology of Langerhans Cell Histiocytosis	221
Laura Schmitz and Blaise E. Favara	
In this article, Langerhans cell histiocytosis (LCH) is described with a nosological perspective. The epidermal Langerhans cell, which most closely resembles the key lesional cell, is characterized. The basic lesion of LCH, its patterns in different sites, diagnostic methods, and results of special studies are detailed. Current concepts of pathogenesis also are discussed.	
Clinical Aspects of Langerhans Cell Histiocytosis	247
Maurizio Aricò and R. Maarten Egeler	
Langerhans cell histiocytosis remains an enigmatic disease with protean manifestations. It may be self-limited in some, whereas in others, even intensive treatment is unsuccessful. The outcome depends on whether vital organ function is compromised at diagnosis or shortly thereafter, in which case the prognosis is grave.	

Langerhans cell histiocytosis in the adult is rare, but it is important to recognize its occurrence, as it must be differentiated from lymphoma, myeloma, and a variety of skin conditions and endocrinopathies. It has been reported in patients up to the ninth decade of life, and occurs equally in men and women. Local disease has a good prognosis, but associated diseases—particularly malignancy—may be the cause of death in some adults. The optimal treatment is not known. Coordinated investigation of the epidemiology and therapy of this disease is needed.

Langerhans Cell Histiocytosis of the Skin**269**

Stephanie Munn and Anthony C. Chu

Cutaneous involvement in Langerhans cell histiocytosis (LCH) occurs in 50% of cases and may be the presenting feature. It is, therefore, important to recognize the wide spectrum of clinical disease that this disorder may adopt in the skin. Cutaneous involvement is not necessarily a benign feature and many patients progress to multi-system disease. There are a number of treatments available for cutaneous LCH. The rationale is to start with the simplest treatment and progress to systemic or interventional therapy as needed.

Central Nervous System Disease in Langerhans Cell Histiocytosis**287**

Nicole G. Grois, Blaise E. Favara, Gerhard H. Mostbeck, and Daniela Prayer

Central nervous system (CNS) disease in Langerhans cell histiocytosis (LCH) is a poorly understood complication of yet unknown frequency. By far the most common manifestation is in the hypothalamic-pituitary system with diabetes insipidus as the leading sign, followed by other endocrinopathies and hypothalamic dysfunction. However, essentially all other parts of the CNS may be involved. On the one hand, space-occupying histiocytic infiltrates may lead to size- and site-dependent symptoms, extending from adjacent bone lesions or arising from the meninges or choroid plexus. On the other hand, a progressive neurological deterioration can occur with mainly cerebellar-pontine symptoms. In this article, these clinical patterns are described in correlation with the morphology on MR imaging and histopathology. Further, the therapeutic strategies are reviewed critically, and guidelines for the management of patients with LCH-related CNS disease are presented.

The Role of Radiology in the Diagnosis and Follow-Up of Langerhans Cell Histiocytosis**307**

James S. Meyer and Beatriz De Camargo

Diagnostic imaging plays a major role in the management of patients with Langerhans cell histiocytosis. Plain radiography

depicts most lesions. Nuclear scintigraphy may detect additional areas of bone involvement, but its routine use is controversial. Ultrasonography may be used to evaluate the abdomen for evidence of solid organ involvement. CT and MR imaging are often of great value in clarifying and delineating findings seen on plain radiographs and other imaging modalities. Ultimately, the choice of imaging study depends on the patient's clinical presentation and the body part affected.

Current Therapy for Langerhans Cell Histiocytosis

327

Valerie Broadbent and Helmut Gadner

The changing concept of the pathogenesis of Langerhans cell histiocytosis over the past 50 years has been mirrored by evolving treatment regimens. The publications by the Histiocyte Society in the 1980s of diagnostic, clinical, and laboratory criteria allowed international collaboration in treatment trials. These, in turn, have allowed stratification of risk groups and the evolution of a salvage therapy protocol for the poorest risk patients. Experimental therapies now being evaluated may be the treatment strategies for the next decade.

Controversies and New Approaches to Treatment of Langerhans Cell Histiocytosis

339

Robert J. Arceci, Malcolm K. Brenner, and Jon Pritchard

There continues to be genuine ambivalence as to whether Langerhans cell histiocytosis (LCH) is a primary neoplastic or immunodysregulatory disorder. Treatment strategies have moved from one camp to the other depending upon the most current alleged successes or failures. This has been particularly true for patients who fall outside of the sphere where treatment is minimal or where known treatment approaches are clearly beneficial. However, there is growing evidence that LCH is both the result of clonal proliferation of Langerhans cells and the immunologic consequence of increased cellular activation. This new knowledge should be the basis for the development of new therapeutic approaches for patients with LCH and its complications.

A Framework for Understanding and Responding to the Psychosocial Needs of Children with Langerhans Cell Histiocytosis and Their Families

359

Steven Simms and Norma J. Warner

This article presents a five-point framework to help health-care providers understand and manage important psychosocial issues related to Langerhans cell histiocytosis (LCH). It entails frank and open discussions with patients and their families of how the disease can affect them individually and collectively. Each point is explained and then applied to two different cases. The framework is applicable to all chronic pediatric diseases, but is particu-

The Relation of Langerhans Cell Histiocytosis to Acute Leukemia, Lymphomas, and Other Solid Tumors: The LCH-Malignancy Study Group of the Histiocyte Society

369

R. Maarten Egeler, Joseph P. Neglia, Maurizio Aricò, Blaise E. Favara, Andreas Heitger, Mark E. Nesbit, and H. Stacy Nicholson

The frequency of Langerhans cell histiocytosis (LCH) and a malignant neoplasm occurring in the same individual appears to be greater than previously recognized. To define the occurrence and the pattern of these events, a Study Group of the Histiocyte Society initiated a registry of patients in whom this association occurred synchronously or asynchronously. Evaluation of 54 patients detected two patterns of associations between LCH and other disorders. First, it is possible that therapy of LCH promotes a secondary malignancy. Second, it is possible that a genetic predisposition, with or without the immunosuppression associated therapy for the malignancy, plays a role in the development and expression of disseminated LCH. Data collected by the LCH-Malignancy Study Group may provide insights into the etiology and pathophysiology of LCH.

The Epidemiology of Langerhans Cell Histiocytosis

379

H. Stacy Nicholson, R. Maarten Egeler, and Mark E. Nesbit

Little progress has been made in finding the cause of LCH. Epidemiologic studies are difficult because of the rarity of the disease. Although several associations have been demonstrated in case-control studies—in particular the association with thyroid disease—no causal relationships have been documented. Additional case-control studies may uncover the to-date missing lead that proves fruitful for epidemiologic investigation.

Langerhans Cell Histiocytosis Research: Past, Present, and Future

385

Christian Nezelof and Françoise Basset

This article reviews the various investigative events that led to the endorsement of the term *Langerhans cell histiocytosis* for the various clinicopathologic conditions previously called *Hand-Schüller-Christian disease*, *Abt-Letterer-Siwe disease*, *eosinophilic granuloma of bone*, and *histiocytosis X*. The different denominations reflect the changing conceptual approaches to the so-called *reticuloendothelial system* and the successive acquisition of new ultrastructural and immunocytochemical data.

Many etiologies have been proposed for Langerhans cell histiocytosis (LCH). Recent scientific studies have clearly provided new insights into the etiology and pathogenesis of the disease. The possible role of viruses has not been completely negated, but no viral genomes have been consistently detected in LCH lesions. Other studies do not indicate that LCH arises from a primary defect in the immune system, although altered immune responses and immune dysfunction may play a role in the pathophysiology of the disease. Definitive results have been gained from molecular studies of clonality, however. These have definitively established that LCH is a clonal histiocytic disease rather than a reactive polyclonal disorder.

Familial Hemophagocytic Lymphohistiocytosis: Primary Hemophagocytic Lymphohistiocytosis

417

Jan-Inge Henter, Maurizio Aricò, Göran Elinder,
Shinsaku Imashuku, and Gritta Janka

Hemophagocytic lymphohistiocytosis represents a spectrum of pathogenetically different diseases including the rapidly fatal autosomal recessive disease of familial hemophagocytic lymphohistiocytosis (FHL). The onset is usually during the first years of life with fever, cytopenia, and hepatosplenomegaly. Neurologic symptoms may supervene. Similar symptoms may occur in the infection-(virus-)associated or malignancy-associated hemophagocytic syndromes (IAHS/MAHS). Triggering infections can be found in all these diseases and do not allow for reliable differentiation. An international treatment protocol (HLH-94) has been developed for FHL, but immunomodulatory treatment may be justified in IAHS and MAHS as well, since they also have a high fatality rate.

Infection- and Malignancy-Associated Hemophagocytic Syndromes: Secondary Hemophagocytic Lymphohistiocytosis

435

Gritta Janka, Shinsaku Imashuku, Göran Elinder,
Marion Schneider, and Jan-Inge Henter

Hemophagocytic lymphohistiocytosis represents a spectrum of pathogenetically different diseases in which a T-cell induced, uncontrolled activation of phagocytosing macrophages may lead to fever, organomegaly, and pancytopenia. The underlying immunologic disturbance can either be genetically transmitted, like in FHL, or acquired, as in IAHS or MAHS. Triggering infections can be found in all these diseases and do not allow a reliable differentiation. An international treatment protocol has been developed for FHL. IAHS and MAHS also have a high fatality

rate, justifying immunomodulatory treatment if the disease is progressive.

Malignant Histiocytosis: Histologic, Cytochemical, Chromosomal, and Molecular Data with a Nosologic Discussion

445

Jean Gogusev and Christian Nezelof

The histologic, chromosomal, and molecular features of malignant histiocytosis (MH) as an entity belonging to the malignant histiocytic disorders are reported in this article. The contributions provided by the MH-derived permanent cell lines are described more specifically. These in vitro studies have demonstrated that the MH proliferation is characterized by a unique chromosomal abnormality, the 5q35 usually associated with a t(2;5) translocation generating a fusion gene NPM/ALK and the subsequent expression of p80 protein. In addition, these in vitro studies have shown that 5q35 proliferative cells are glass adherent, can develop an immunodependent phagocytosis, and are able to reduce NBT and produce TNF- α . Remarkably, they express constitutively c-fms, the receptor of the macrophage growth factor, and under phorbol diester stimulation, are able to modulate the expression of this receptor and its ligand as well as TNF- α and IL-1. An important part of the article is devoted to the nosological discussion concerning the conceptual controversy about the T-lymphoid or histiocytic origin of the proliferative cells.

Malignant Histiocytic Disorders in Children: Clinical and Therapeutic Approaches with a Nosologic Discussion

465

Peter Bucsky and R. Maarten Egeler

Malignant histiocytic disorders, other than leukemias, are extremely rare in childhood. Despite unresolved nosologic and terminologic difficulties, they should be classified according to the lineage of the aberrant cells in a given tumor. There are no common and typical clinical presentations, nor are there established treatment modalities available. For the disseminated forms, aggressive systemic treatment modalities—similar if not identical to those used for large cell anaplastic lymphomas—appear to be the best treatment option. For the localized forms, which are primarily dendritic cell sarcomas, a more localized and individualized therapy is appropriate.

Epilogue

473

Stephan Ladisch

Index

477

Subscription Information

Inside back cover