15 Histiocytic disorders

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Introduction

The histiocytoses are a diverse group of hematologic disorders defined by the pathologic infiltration of normal tissues by cells of the mononuclear phagocyte system (MPS). The heterogeneity of this family of disorders, a direct result of the biologic variability of the cells of the MPS and the tissues they inhabit, makes the study of these diseases one of the most intriguing yet complex areas of modern hematology.

Advances in basic hematology and immunology over the last two decades have significantly enhanced our understanding of the histiocytic disorders. It is now accepted that the pathogenic cells central to the development of the histiocytoses arise from a common hematopoietic progenitor. More specifically, the ability to molecularly identify the hematopoietic cells has enabled us to classify the histiocytoses based on the cellular basis of the disease and to define the natural history of these disorders.[1,2] These pathologic cells phenotypically resemble immature mononuclear phagocytes at specific stages of differentiation.[77]

The Histiocyte Society, formed in 1985, has served as a forum for enhanced collaboration between international histiocytosis experts. Since its inception, the Histiocyte Society has used the cellular based classification of the histiocytoses as a guideline for therapeutic studies, which have in turn significantly advanced our ability to care for patients, improve their outcomes and advance the scientific understanding of the histiocytoses. In this chapter we use the cellular classification of histiocytic disorders, as adopted by the Histiocyte Society, to present each subgroup of this family of disorders, describe their natural history and present current therapeutic approaches and outcomes.

Histiocytes and normal immune function

The MPS is a system of cells whose primary function consists of phagocytosis of foreign material, antigen processing, and antigen presentation to lymphocytes. This system, recognized in part through the work of Metchnikoff, was originally termed the reticuloendothelial system by Ludwig Aschoff in the early part of the twentieth century.[3,4] The central cell of this system, the mononuclear phagocyte or histiocyte, represents a group of anatomically and functionally distinct cells arising from a common precursor, the hematopoietic stem cell.

Cells of the MPS have a wide range of morphologic, anatomic and functional characteristics that make classification of this system difficult. Our ability to identify and classify the cells of the MPS has advanced in parallel with developments in basic hematology and immunology. As our knowledge of the molecular biology regulating hematopoiesis has improved, we have been able to identify specific characteristics that have enabled us to classify the cells of the MPS. Mononuclear phagocytes can be divided into two major classes, macrophages and dendritic cells. This classification is based on (i) phagocytic and antigen-presenting abilities, (ii) morphologic and ultrastructural appearance, (iii) expression of common enzymes, (iv) presence of common cell surface antigens, and (v) common regulatory cytokine and transcription factor networks.

Tissue macrophages are derived from bone marrow hematopoietic precursors and can arise directly from circulating peripheral blood monocytes. These cells enter different tissues and assume tissue-appropriate morphology based on the local cytokine milieu. Once established in various tissues, macrophages typically do not have the ability to self-renew extensively except possibly under specialized microenvironments such as in the lungs and pituitary. Tissue inflammation increases the influx of monocytes, which in turn give rise to macrophages with an immunologically activated phenotype. Inflammatory stimuli can also further enhance the local replication of macrophages in cases of tissue injury.[5,6] Regardless of location, macrophage growth and differentiation is a tightly controlled process regulated by specific growth factors.

Interleukin (IL)-3, IL-4, IL-13, granulocyte–macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) are all stimulatory cytokines with a major role in macrophage development and differentiation.[6] M-CSF activity is especially essential for appropriate macrophage growth and differentiation. The M-CSF receptor, a product of the c-*fms* protooncogene, is expressed by most members of the MPS. When bound by M-CSF this receptor dimerizes, leading to the activation of its kinase domain and initiation of downstream signaling pathways. The signaling cascade initiated by the binding of M-CSF to its receptor is essential for the proliferation of progenitor cells of the monocyte–macrophage lineage, differentiation and their long-term survival. Information regarding the role of M-CSF primarily arises from studies of *op/op* knockout mice, which are deficient in the M-CSF receptor.[7] Despite their severe monocyte–macrophage deficiencies, *op/op* mice maintain normal levels of dendritic cells in their spleens and skin, thus demonstrating an alternative and M-CSF-independent pathway for their development.[8,9] The GM-CSF receptor, also present on most members of the MPS, plays a critical role in normal cellular homeostasis, differentiation and function.[8] There is also a positive survival effect of stem cell factor (the ligand for the c-KIT receptor) and FLT3 ligand and its cognate receptor FLT3, as well as inhibitory roles for interferon (IFN)-α/β, transforming growth factor (TGF)-β and leukocyte inhibitory factor as critical determinants in macrophage development.[6] The phenotypic and functional heterogeneity of macrophages as a group is attributed to the tissue-specific effects of cytokine stimulation on the multipotent monocyte. Pathologic changes in this cytokine milieu play important roles in the pathogenesis of the histiocytoses.[10,14]

Macrophages are ubiquitously distributed in the body and are heavily represented in mucosal tissues and other potential portals of entry for microorganisms, where they function in both innate and adaptive immunity. They have the capacity to phagocytose foreign organisms and release inflammatory cytokines that in turn recruit other inflammation-associated cell types. Macrophages also maintain the ability to process and present antigenic portions of foreign organisms to T lymphocytes, although not as effectively as dendritic cells. Tissue macrophages have significant functional variability depending on their location within the body. Peritoneal and soft tissue macrophages, Kupffer cells, foam cells, synovial cells, osteoclasts and microglial cells are all members of this class of cells and contribute to tissue growth, repair and remodeling. A distinguishing feature of macrophages is expression of the enzymes lysozyme, α_1-antitrypsin, α_1-antichymotrypsin, aminopeptidase, peroxidase, alkaline phosphatase, α-naphthol-chloroacetate esterase and β-glucuronidase.

The second class of mononuclear phagocytes, the dendritic cells, was first described by Steinman and Cohn in 1973. These cells were named because of their unique membranous, and often branch-like, cytoplasmic aberrations (from the Greek word for tree, δενδρεον).[15] Dendritic cells are primarily located in skin, mucosa, bone marrow, spleen, thymus and lymph nodes. This group of cells also includes dendritic cells of the lymphoid follicle, the interdigitating dendritic cells of the paracortical regions of lymph nodes, and Langerhans cells of the skin and other organs. Langerhans cells, originally identified by Paul Langerhans in the late 1800s, are mononuclear cells with little cytoplasmic vacuolization and a folded or indented nucleus. Electron microscopic observation of Langerhans cells reveals the presence of Birbeck granules, a distinguishing characteristic of these cells. Birbeck granules, or X bodies, are rod-shaped, pentalaminar, cytoplasmic inclusions, typically ending in a vesicular structure that arise as a result of receptor-mediated endocytosis and are involved in antigen processing.[16]

In contrast to macrophages, dendritic cells are less phagocytic but play a central role in initiating primary T-lymphocyte antigen responses. The hallmark of dendritic cells is their conversion from immature, peripherally located sentinels capable of antigen capture and processing to mature immunostimulatory cells, a process called *maturation*. This specific characteristic of dendritic cells, in combination with their ability to migrate, provides a physical and functional link between peripheral tissues and secondary lymphoid organs where lymphocyte maturation takes place.[17] Langerhans cells and the interdigitating dendritic cells present antigens to stimulate primary T-lymphocyte responses. It is well established that the precursor to most dendritic cells is bone marrow derived but the biologic significance of this differentiation schema is still not completely defined as a significant amount of the data has been derived from *in vitro* studies.[16] Other distinguishing characteristics of mature dendritic cells include (i) high expression levels of class II major histocompatibility complex (MHC) antigens and costimulatory receptors, making them potent at antigen presentation, (ii) adenosine triphosphatase and α-mannosidase expression and (iii) distinct paranuclear and cell surface-staining pattern with peanut agglutinin that contrasts with the diffuse staining pattern demonstrated by macrophages.[16,18]

The development of methods to generate monoclonal antibodies in the 1970s and 1980s significantly enhanced our knowledge of the MPS. The F4/80 antibody, a murine pan-macrophage antibody, was one of the first well-recognized markers of the MPS. This antibody recognizes members of a gene family that includes the human epidermal growth factor (EGF) module-containing mucin-like hormone receptor 1 and CD97. The presence of this antigen on the surface of tissue macrophages and dendritic cells helped confirm the existence of a common origin for the diverse lineages that comprises the MPS. Other markers such as S-100β subunit, CD1a and Langerin, are found on Langerhans cells but are usually absent on macrophages are used clinically to distinguish

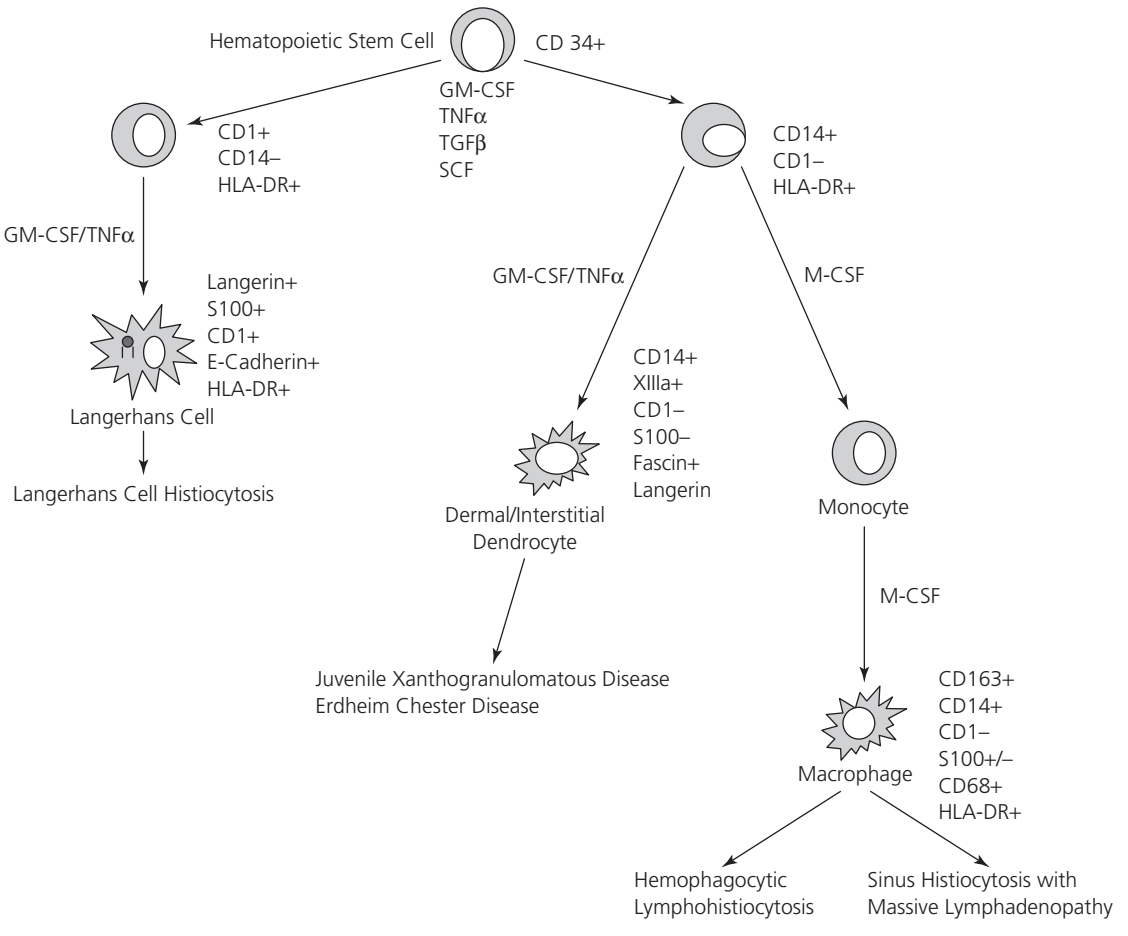

Fig. 15.1 Possible lineage relationships of hematopoietic cells and cells of the mononuclear phagocyte system along with the histiocytic disorders that arise from them. GM-CSF, granulocyte–macrophage colony-stimulating factor; M-CSF, macrophage colony-stimulating factor; SCF, stem cell factor; TGF, transforming growth factor; TNF, tumor necrosis factor. Adapted with permission from Ref. 3.

between the cells of the MPS. Conversely, monocytes and macrophages express nonspecific carcinoembryonic cross-reacting antigen, CD4 antigen, nonspecific esterase and the cell surface marker CD11c (Leu-M5). Both types of cells express class II MHC molecules and T-lymphocyte costimulatory receptors. These markers, in particular S100, CD1a and Langerin are utilized clinically to distinguish between the different histiocytic syndromes. Figure 15.1 denotes the lineage relationships thought to define the differentiation of cells of the MPS and the developmental stages from which various histiocytic disorders are believed to arise.

The development and differentiation of the cells of the MPS, much like other hematopoietic lineages, is driven by a tightly regulated pattern of gene expression governed by distinctive sets of transcription factors that control cell proliferation and differentiation. The main transcription factor families implicated in the development of this system include the *myb* family, the *Ets* family and the C/EBP family. PU.1, a member of the *Ets* family, plays a central role in monocyte–macrophage lineage as demonstrated by PU.1 knockout mice which lack functional monocytes and tissue macrophages and display significant dendritic cell abnormalities.[19,21] This has become clearer recently as it has been shown that PU.1 regulates the expression of c-*fms*, the gene coding for the M-CSF receptor, in addition to other critical genes such as FcγRI, FcγRIIIA, scavenger receptors type 1 and 2, CD11b, CD18 and CD14.[21]

In summary, the MPS represents a continuum of functionally distinct cell types that arise from common bone marrow progenitors and differentiate along specific lineage pathways based on environmental stimuli and intrinsically regulated gene expression patterns. The result is the generation of a diverse group of cell types with distinct but often overlapping biologic functions. Understanding this biologic heterogeneity is an important key to more accurate diagnosis and treatment of the histiocytic disorders.

Modern classification of histiocytic disorders

As proposed in 1987,[1] the histiocytic disorders can be

classified into three classes based on the pathologic cells present within the lesions.

- Class I: Langerhans cell histiocytoses and other dendritic cell disorders.
- Class II: non-Langerhans cell histiocytoses primarily consisting of hemophagocytic lymphohistiocytosis.
- Class III: malignant histiocytosis.

This system was revised in 1997 by the World Health Organization's Committee on Histiocytic/Reticulum Cell Proliferations and the Reclassification Working Group of the Histiocyte Society. The central theme of this reclassification schema consisted of distinguishing the clearly malignant histiocytoses from the remaining subtypes, the so-called "disorders of varied biological behavior". Acute myelomonocytic leukemia (FAB M4), acute monocytic leukemia (FAB M5), chronic myelomonocytic leukemia and the histiocytic sarcomas are all classified in the malignant histiocytoses category. The disorders of varied biological behavior continued to be divided into dendritic cell-related disorders (class I) and macrophage-related disorders (class II). The dendritic cell-related disorders include Langerhans cell histiocytosis, the most common type in this class, in addition to other less common subtypes. Primary and secondary hemophagocytic lymphohistiocytosis, in addition to sinus histiocytosis with massive lymphadenopathy (also known as Rosai–Dorfman disease), are the two major types of macrophage-related histiocytosis discussed in this chapter. This classification schema is summarized in Table 15.1.[2] The remainder of this chapter focuses on the pathophysiology, clinical presentation, treatment and outcomes of the principal histiocytoses.

Table 15.1 Classification of histiocytic disorders.

Class I: dendritic cell histiocytoses
Langerhans cell histiocytosis
Secondary dendritic cell processes
Juvenile xanthogranuloma and related disorders
Erdheim–Chester disease
Solitary histiocytomas of various dendritic cell phenotypes
Class II: nondendritic cell histiocytoses
Primary hemophagocytic lymphohistiocytosis
Familial hemophagocytic lymphohistiocytosis
Secondary hemophagocytic lymphohistiocytosis
Infection associated
Malignancy associated
Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy)
Solitary histiocytoma with macrophage phenotype
Class III: malignant histiocytoses
Monocyte related
Leukemias (FAB and revised FAB classification)
Monocytic leukemia M5A and M5B
Acute myelomonocytic leukemias M4
Chronic myelomonocytic leukemias
Extramedullary monocytic tumor or sarcoma
Dendritic cell-related histiocytic sarcoma
Macrophage-related histiocytic sarcoma

FAB, French–American–British.

Disorders of varied biological behavior: dendritic cell-related (class I) histiocytoses

Langerhans cell histiocytosis

Biology

Langerhans cell histiocytosis (LCH) is the most common member of the dendritic cell-related histiocytic disorders. LCH includes the previously identified disorders known as eosinophilic granuloma, Abt–Letterer–Siwe disease and Hand–Schüller–Christian disease. The pathologic similarity of these disorders was first noted by Sidney Farber in 1941 and by the 1950s, as a result of the work of Lichtenstein, these disorders were collectively referred to as histiocytosis X.[16] The persistent use of this historical terminology in modern medical vernacular is indicative of its significance and utility for cataloging patient symptomatology. Regardless of the historical eponyms, the pathologic hallmark of all subtypes of LCH is the abnormal proliferation and accumulation of immature Langerhans cells along with macrophages, lymphocytes and eosinophils that together form granulomatous lesions. Although the biologic role of LCH cells in the pathogenesis of LCH remains unclear, it is now generally accepted that the close physical interaction between these cells and other cell types present in these lesions is associated with an abnormal cytokine and chemokine microenvironment that underlies the pathogenesis of LCH.

In 1973 Nezelof *et al*.[22] provided definitive evidence for the phenotypic similarity of normal Langerhans cells and LCH cells, including a description of the presence of Birbeck granules in both cell types. However, LCH cells, in contrast to normal Langerhans cells, typically lack dendritic cell extensions and have a rounded appearance with distinct cellular margins. These cells express CD1a, S100 and Langerin (CD207) but not the typical markers of more mature dendritic cells such as CD83, CD86 and DC-Lamp (Fig. 15.2). In addition, these cells express CD40 and intracellular MHC class II proteins but are inefficient antigen-presenting cells. When LCH cells are exposed *in vitro* to CD40L they acquire markers of dendritic cell maturation.[23] LCH cells also express CCR6, the receptor for the proinflammatory chemokine CCL20/MIP3α, a characteristic of immature dendritic cells. Furthermore, these cells have been shown to also secrete CCL20/MIP3α, CCL5/RANTES and CXCL11/I-TAC, all of which are believed to function in recruiting additional LCH cells, eosinophils and T cells to LCH lesions.[12] Of note, the co-expression of CCR6 and CCR7 on LCH cells has also been reported. This may be suggestive of the pathological

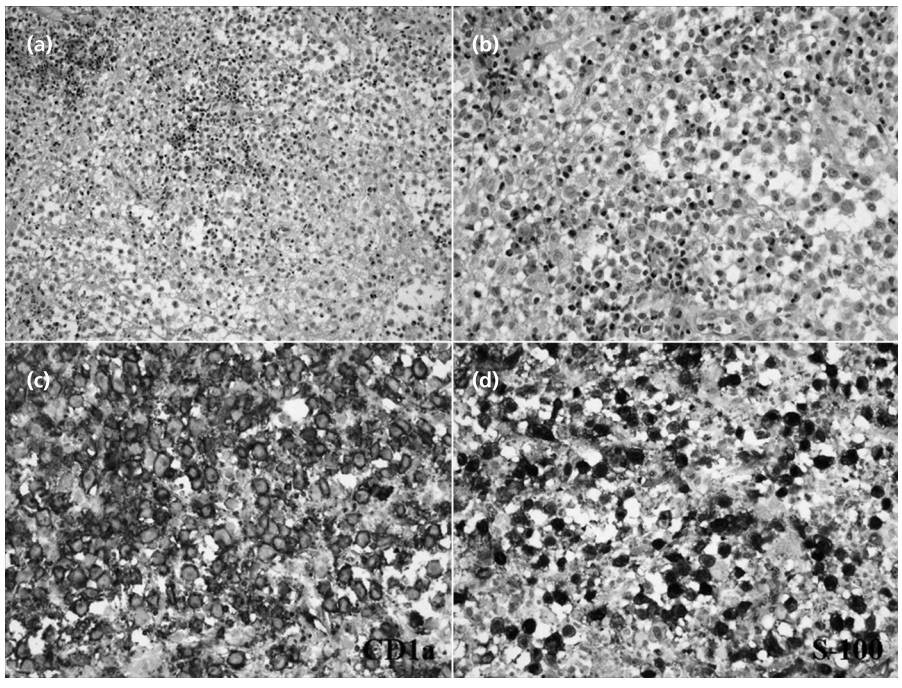

Fig. 15.2 Langerhans cell histiocytosis. Histology and immunohistochemical staining of a bone lesion (eosinophilic granuloma) characterized by (a, b) sheets of large pale Langerhans cells, many of which have prominent nuclear indentations or grooves, interspersed with large numbers of bilobed eosinophils (hematoxylin and eosin staining) (original magnification: a, ×200; b ×400). Langerhans cells strongly express CD1a (c, original magnification ×400) and S100 protein (d, original magnification ×400). Photographs courtesy of Dr John Reith, Department of Pathology, University of Florida School of Medicine, Gainesville, FL, USA.

maturational arrest of these cells.[14] Immunohistochemical and *in situ* hybridization data also demonstrate abnormal release of specific cytokines, such as GM-CSF, IL-10, TGF-α/β, IFN-γ and tumor necrosis factor (TNF)-α, by lesional cells in LCH.[13,24,25] The cytokine abnormalities noted in LCH lesions are hypothesized to magnify the local autocrine and paracrine effects of these cells, resulting in a focal "cytokine storm". These cytokines also cause local tissue damage and contribute to the systemic symptoms such as fever, skin rashes and hypotension.[16,24] Unlike hemophagocytic lymphohistiocytosis, there is no clear-cut evidence for systemic cytokine overproduction in most cases of LCH.

Despite our improved understanding of the molecular events involved in the pathophysiology of LCH, its etiology remains undetermined. Infectious, inflammatory and neoplastic mechanisms have all been postulated to play an etiologic role in LCH, but the relative contribution of each process to the development of the disease remains controversial.[10,11,16,26–28] The human androgen receptor DNA assay and analyses of T-cell receptor gene rearrangements for detecting clonality have demonstrated the clonal nature of LCH cells but not lymphocytes in lesions, a finding consistent with a neoplastic origin for LCH.[29,30] This is further supported by analyses of LCH lesions using comparative genomic hybridization and loss of heterozygosity, which reveal multiple chromosomal abnormalities.[31,32] Clinical evidence of familial cases, in addition to the increased risk of malignancy seen in patients with histiocytosis, further supports a neoplastic origin for some forms of LCH.[33,34]

However, this conclusion is tempered by several lines of evidence suggesting an inflammatory contribution to the etiology of LCH. *In vitro* studies have demonstrated an inability to grow LCH cells in culture or in immunodeficient mice, characteristics typically observed with aggressive malignancies. Studies of isolated pulmonary LCH show no consistent or uniform evidence of clonality. Immunohistochemical evidence for human herpesvirus-6 in bone lesions, in addition to differences in HLA types among patients with single-system versus multisystem LCH, might be considered suggestive of a potential inflammatory etiology for LCH, although these data remain controversial due to methodologic issues and inconsistencies.[32,35,36] Implications of the variable expression pattern of MDM2, p53 and p21 and the strong expression of TGF-β seen in LCH remain unclear.[11,37] Based on this data, most experts now agree that LCH is the result of complex interactions between environmental factors and intrinsic genetic changes leading to a clonal proliferative disorder of immature Langerhans cells with variable clinical behavior.[10,11,16,26–28,38,39] Although the pathologic findings may not be clearly different among cases of LCH, the clinical variability strongly suggests different biology and thus a possible continuum from the least to the most aggressive forms of the disease.

Incidence and epidemiology

LCH has been historically considered a disease of young children, with a peak occurrence between the ages of 1 and 3 years. A Danish study estimated the incidence of LCH in children less than 15 years old to be 0.54 per 100 000 children per year. However, this is considered to be an underestimation as a proportion of children are believed to go undiagnosed. A Swedish study has estimated an incidence of

around 0.9 per 100 000.[40,41] LCH also shows a predilection for males, with a female to male ratio of 1 : 1.2–2.1.[16,41] It is also now well recognized that the incidence of LCH in adulthood is likely to be underestimated. This has been attributed to the multiple subspecialties involved in the care of patients with this disease depending on the involved organ system in addition to incorrect diagnoses.[41] This problem is now being addressed by the Histiocyte Society as more emphasis is being placed on studies of adult subjects, including the most recent adult therapeutic study, LCH A-1.

A case–control epidemiologic study has suggested associations between the diagnosis of LCH and maternal urinary tract infections as well as feeding problems, medication use and blood transfusions during the first 6 months of life.[42] A subsequent study has demonstrated a significant odds ratio for postnatal infections, diarrhea and vomiting, as well as medication use in multisystem LCH, while single-system LCH was associated with thyroid disease or a family history of thyroid disease.[43] The results of these studies are for the most part inconclusive with regard to any etiologic associations. However, it has to be pointed out that none of the studies performed has noted a geographical or seasonal clustering of cases of LCH, making a common infectious etiology unlikely.

Clinical presentation and therapy

LCH represents a wide variety of different clinical entities recognized to be pathologically the same. LCH is clinically subclassified by the degree and location of organ involvement: localized single-system disease, multifocal single-system disease and multisystem disease. The location of involvement has been shown to be of prognostic importance, with bone marrow, pulmonary, spleen and liver involvement denoted as "risk organs" while involvement of cranial bones or spine with extradural soft tissue extension is considered to be "central nervous system (CNS) risk".[44,45] This clinical classification schema currently serves as the basis for risk stratification of LCH treatment protocols.

At the time of diagnosis, a complete work-up should be performed to establish the full extent of disease and delineate risk-based therapy (Table 15.2). The work-up should include detailed history and physical examination, complete blood count and differential, metabolic panel including liver and renal function tests, bone scan, skeletal survey and chest radiograph. Urine analysis should also be performed to assess for diabetes insipidus and possible hypothalamic–pituitary involvement. Additional studies such as water deprivation test, antidiuretic hormone levels or other endocrinologic examinations evaluating hypothalamic–pituitary function may be necessary depending on a patient's clinical presentation. Magnetic resonance imaging (MRI) of the brain with gadolinium contrast is becoming a more common part of the staging work-up of "CNS-risk" patients because of the recognition of significant CNS involvement. Bone marrow studies, computed tomography (CT) of the chest and pulmonary function tests should also be performed as clinically indicated to evaluate risk-organ involvement. The role of positron emission tomography remains undefined, but is a potentially promising imaging approach.[46]

Localized LCH involving skin, lymph node or skeleton usually carries a good prognosis. Lesions of bone, a condition often referred to as eosinophilic granuloma, usually present as a painful swelling. These lesions appear radiographically as "punched-out" sites and most commonly affect the calvarium (Fig. 15.3), although they can involve any part of the skeleton. Vertebra plana, or a collapsed vertebra, is a common presentation of this disease process (Fig. 15.4). Single bone lesions rarely need therapy beyond biopsy or curettage, except in the case of severe symptoms or danger of organ dysfunction, such as spinal cord compression or loss of vision. Treatment options for these patients with nonemergency single bone lesions that recur or remain clinically problematic after surgery include nonsteroidal antiinflammatory agents or local steroid injections and, rarely, local low-dose radiation therapy (40–80 cGy). Full surgical resection (i.e., performing a "cancer operation") of these single bone lesions, especially when other vital structures could be compromised as a result of such an operation, is not typically necessary.

Skin disease typically involves the scalp, retroauricular area, neck, upper chest, axilla and groin. This rash can vary from maculopapular to more eruptive and even nodular in appearance (Fig. 15.5). In some patients, the rash can be quite erosive and a risk factor for serious superinfection. Therapy

Table 15.2 Risk groups as defined by the LCH-III protocol (adapted from the Histiocyte Society LCH-III study).

Group 1: multisystem "risk" patients
Multisystem patients with involvement of one or more "risk" organs (i.e., hematopoietic system, liver, spleen or lungs)
Group 2: multisystem "low-risk" patients
Multisystem patients with multiple organs involved but without involvement of "risk" organs
Group 3: single-system "multifocal bone disease" and localized "special site" involvement
Patients with multifocal bone disease (i.e., lesions in two or more different bones)
Patients with localized special site involvement, such as "CNS-risk" lesions with intracranial soft tissue extension or vertebral lesions with intraspinal soft tissue extension

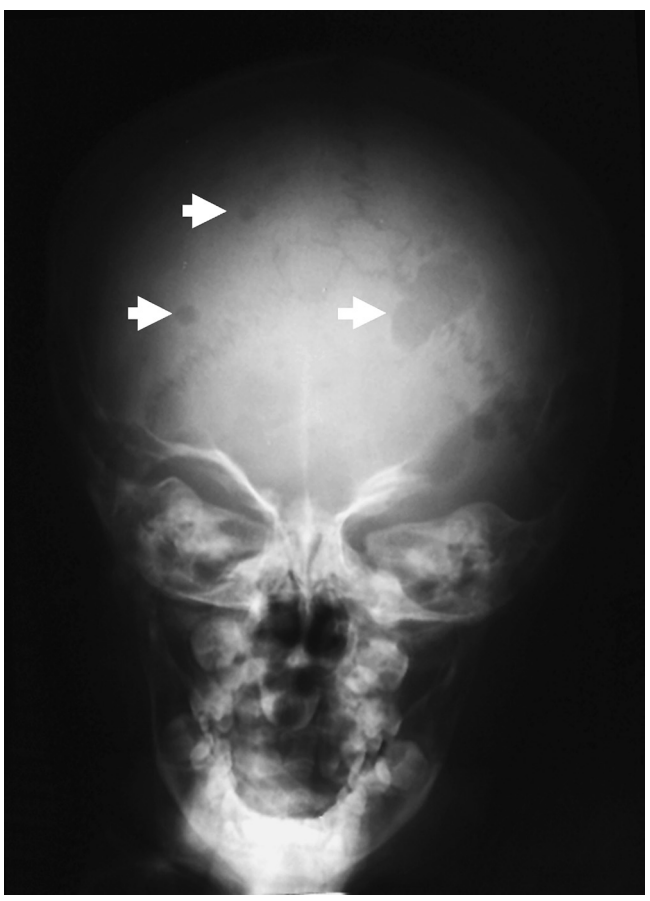

Fig. 15.3 Radiograph of skull of a patient with Langerhans cell histiocytosis showing multiple lytic lesions (white arrows).

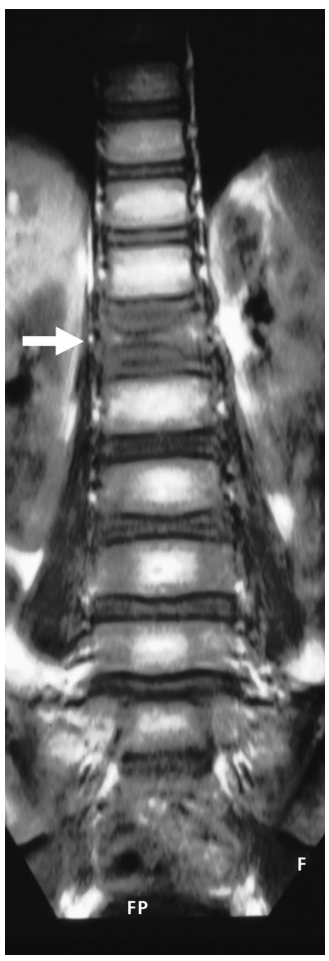

Fig. 15.4 Magnetic resonance image depicting a vertebra plana secondary to involvement of the vertebral body with Langerhans cell histiocytosis (white arrow).

for isolated skin disease typically involves topical steroids or, in some steroid-refractory cases, topical nitrogen mustard, PUVA or short-wave ultraviolet light without psoralen. Systemic steroids and vinblastine are reserved for extensive single-system disease, including skin involvement, usually with good outcomes.[38]

In contrast to localized LCH, systemic therapy is indicated in patients with multisystem LCH. The most common presentation of multifocal LCH includes diffuse skin and multifocal bone involvement. The oral cavity, lymph nodes and, to a lesser extent, the lungs, liver and brain are other common sites of involvement in this disease. Oral cavity involvement can lead to infiltrative lesions with ulceration as well as erosion of the mandible or maxilla, leading to "floating" teeth. Figure 15.6 demonstrates the characteristic CT findings of lung involvement. Diabetes insipidus, with pituitary involvement (Fig. 15.7), is the most common manifestation of CNS involvement in LCH and is reported in 5–30% of patients. The triad of lytic skull lesions, exophthalmos and diabetes insipidus, historically referred to as Hand–Schüller–Christian disease, is not commonly observed at the time of diagnosis, although the chronic waxing/waning course is frequently seen in this group of patients. Risk factors for the development of diabetes insipidus have been reported to include the presence of multisystem disease and craniofacial lesions, especially involving the orbit, ear and oral cavity.[47] In addition to acute CNS involvement, patients with LCH may develop a severe neurodegenerative process involving loss of motor functions and cognition. This syndrome characteristically involves the cerebellum, pons and midbrain, often in a symmetric pattern (Fig. 15.8).[48–50] The clinical severity of neurodegenerative-associated LCH can be independent of radiographic findings or progression.[49,51] There are currently no effective means of ameliorating the progression of this process. Liver involvement is another complication of LCH that portends a poor prognosis. Transaminitis and hyperbilirubinemia are the hallmarks of acute liver involvement in LCH. Patients with hepatic LCH or with multisystem disease appear to have a higher risk of developing sclerosing cholangitis that can, in turn, lead to hepatic fibrosis, liver failure and the need for liver transplantation.

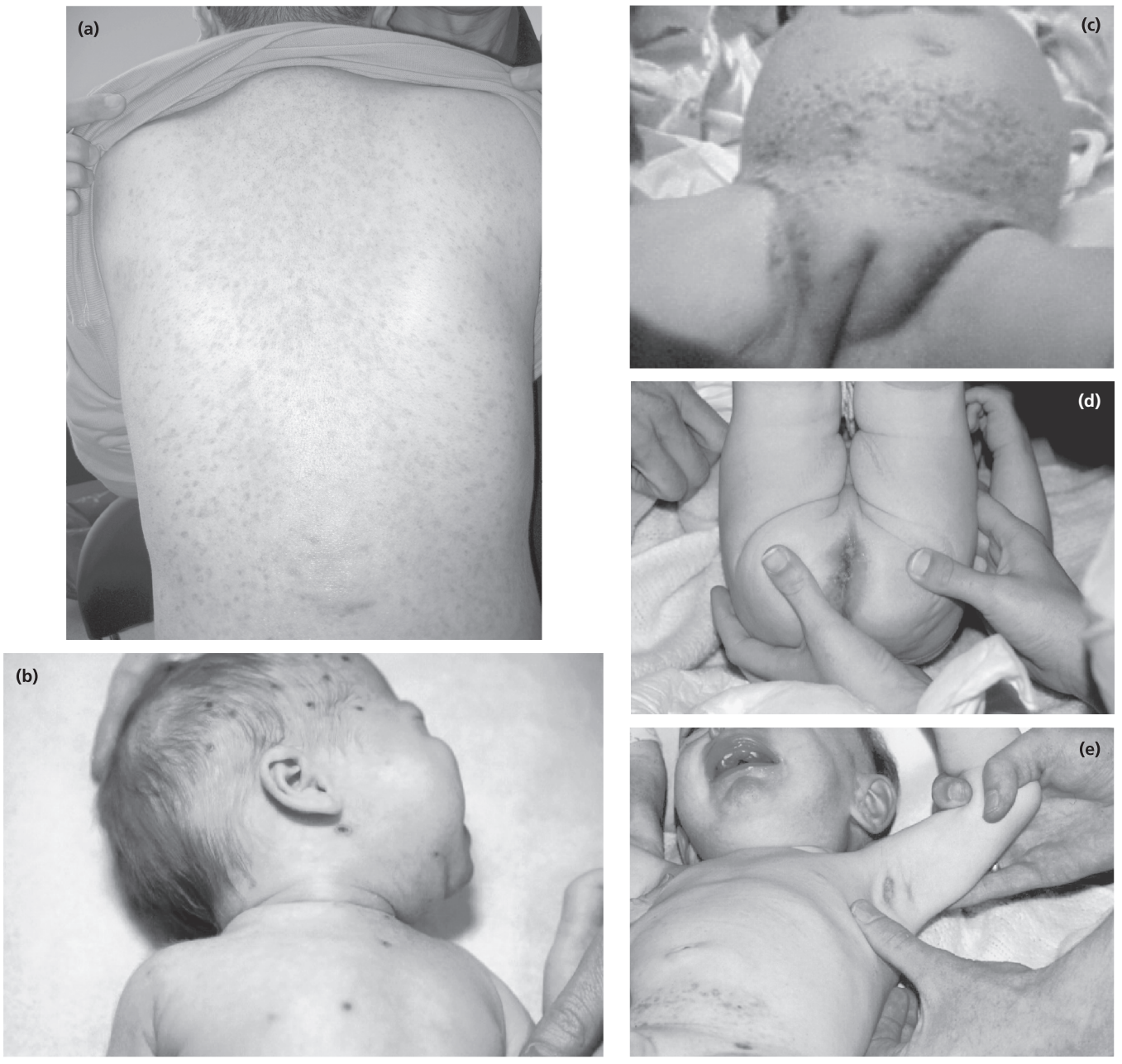

Fig. 15.5 Various depictions of skin involvement with Langerhans cell histiocytosis. (a) The back of a teenager showing slightly raised lesions. (b) Papular appearing lesion in an infant. (c) Inguinal involvement in an infant. (d) Perianal involvement in an infant. Reproduced with permission from Arceci RJ. Histiocytosis. In: Young NS, Gerson SL, High KA (eds) *Clinical Hematology*. Mosby/Elsevier, 2006. (e) Axillary, lower abdomen and oral involvement in an infant. Reproduced with permission from Ref. 39.

In addition to site of involvement, age has been thought to be an important prognostic factor in LCH, with younger patients having a significantly higher mortality rate. However, more recent clinical trial data have shown that response to initial (6–12 weeks) therapy with vinblastine and steroids is the most powerful prognostic factor, outweighing even age. Abt–Letterrer–Siwe disease is a historical eponym used to describe systemic LCH characterized by extensive skin, bone marrow, spleen, liver and lung involvement; it is usually observed in children less than 2 years old. Oral cavity and gastrointestinal involvement are other commonly seen manifestations of this severe form of LCH. Patients typically suffer from intractable fevers, failure to thrive and, in later phases of the disease, severe pancytopenia and hepatic failure leading to hemorrhage and sepsis. Abt–Letterrer–Siwe disease carries a particularly poor prognosis in patients with

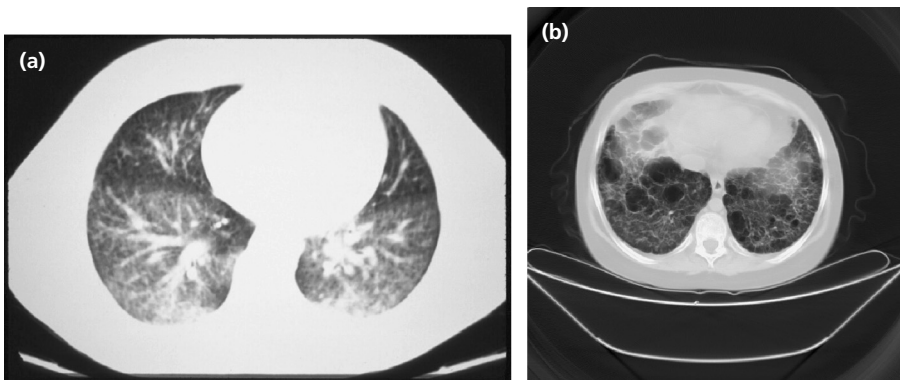

Fig. 15.6 Involvement of the lung in Langerhans cell histiocytosis. (a) Acute nodular involvement; (b) cystic changes often associated with chronic involvement. Photograph (b) courtesy of Dr William Cumming, Department of Radiology, University of Florida School of Medicine, Gainesville, FL, USA.

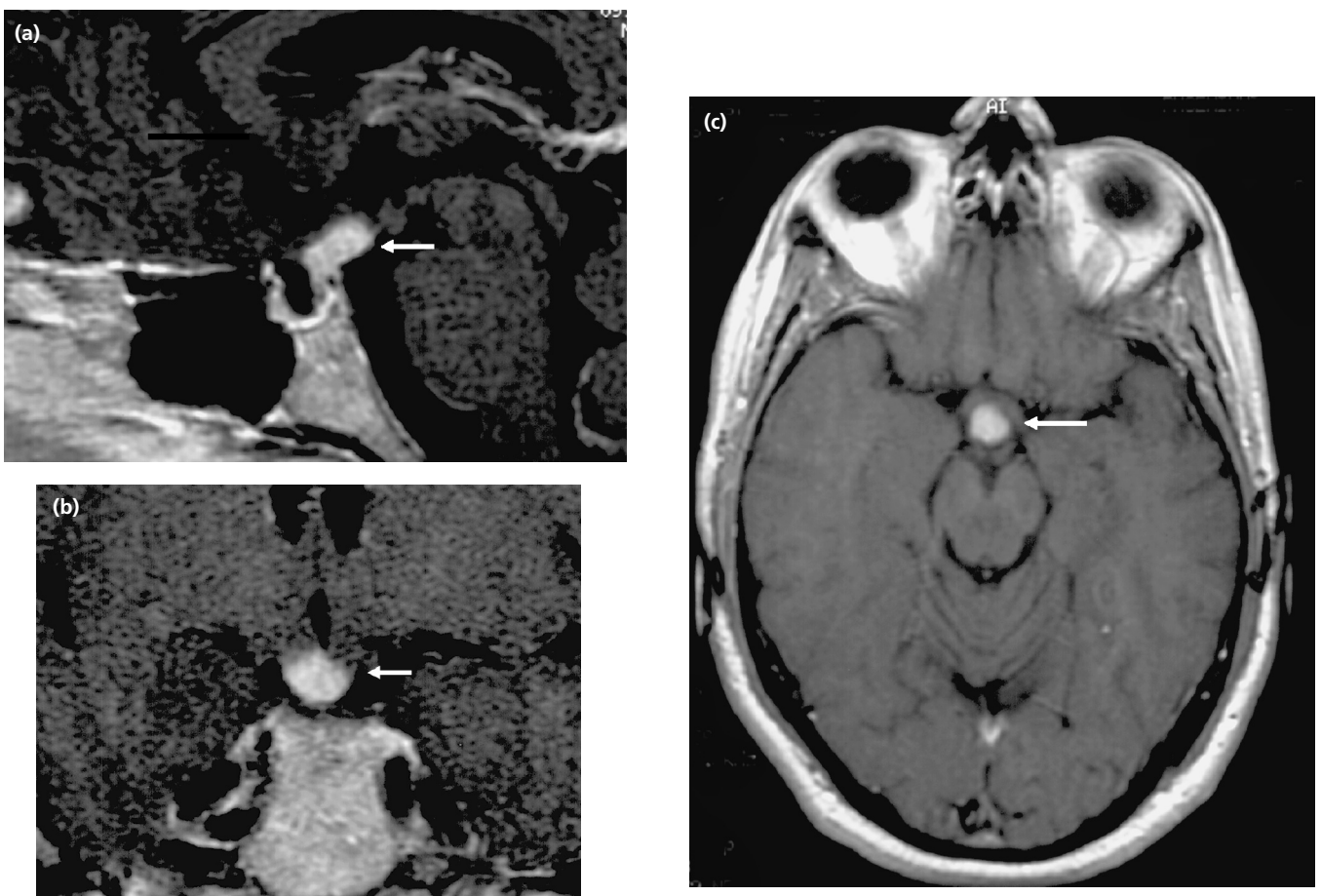

Fig. 15.7 Magnetic resonance image of pituitary involvement in Langerhans cell histiocytosis: (a) sagittal view; (b) coronal view; (c) horizontal view.

advanced hematopoietic involvement who do not show a good response to initial therapy. Patients with Abt–Letterer–Siwe disease should undergo a full evaluation for congenital and acquired immunodeficiency syndromes in addition to infectious etiologies as part of their diagnostic work-up.

It is critical that pulmonary involvement as part of multisystem disease be distinguished from isolated pulmonary LCH (PLCH). PLCH is distinguishable from other forms of LCH by its almost exclusive occurrence in young adults and close association with smoking. PLCH can cause severe inter-

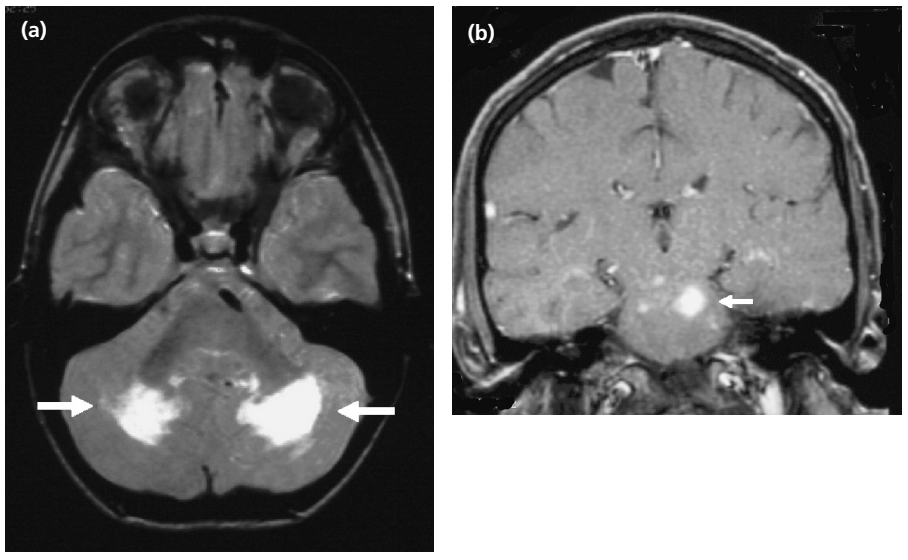

Fig. 15.8 Magnetic resonance image of neurodegenerative disease in an adult patient with Langerhans cell histiocytosis. (a) Symmetric enhancing lesions involving the cerebellar peduncles on a horizontal view; (b) enhancing lesions involving the pons on a coronal view.

stitial lung disease, cor pulmonale and eventual respiratory failure necessitating lung transplantation. The first line of therapy for PLCH remains smoking cessation, followed in some patients with steroids. The role of chemotherapy in PLCH remains uncertain as prospective data are not available. The use of 2-chlorodeoxyadenosine (2-CDA) has shown some promise in PLCH, although this therapy is reserved for patients with refractory disease and has only shown anecdotal success.[52–54] The Histiocyte Society trial for adults with LCH includes patients with PLCH.

Patients with multisystem LCH have been demonstrated to benefit from systemic chemotherapy. The current therapeutic regimens evolved from work originally performed in the 1970s and 1980s. Several studies during that time demonstrated that single-agent therapy with drugs such as methotrexate, vincristine, vinblastine, etoposide, 6-mercaptopurine and prednisone was effective treatment for LCH. These trials were subsequently followed by the larger studies (AIEOP-CNR-HX and DAL-HX 83/90), all of which used regimens with multiple agents. These studies demonstrated response rates of 60–90% using combinations of vinblastine and/or etoposide plus prednisone. These studies also demonstrated that patients with extensive disease and organ dysfunction had significantly higher mortality and recurrence rates.[38,55,56]

The AIEOP-CNR-HX and DAL-HX-83/90 studies were then followed by the first international, prospective, randomized study, LCH-I, which also represented the first international clinical trial of the Histiocyte Society. The results of this study demonstrated that patients randomized to treatment with etoposide plus steroids did not have a better outcome than those randomized to receive vinblastine plus steroids. In addition, this study revealed that response at 6 weeks was strongly predictive of overall outcome. For example, patients without a response to therapy after 6 weeks had a survival rate of less than 40% at 5 years. Another critical outcome of this study was the confirmation of earlier work by Lahey that patients older than 2 years of age and without pulmonary, hepatosplenic or hematopoietic involvement had an excellent prognosis, with a response rate of 90% and survival of 100% at 6 years.[57,58] In comparison with the AIEOP-CNR-HX and DAL-HX 83/90 trials, LCH-I showed a higher recurrence rate and higher frequency of diabetes insipidus. This raised the question of whether more aggressive therapy in patients with high-risk disease would provide a therapeutic advantage.[59]

The second Histiocyte Society protocol, LCH-II, attempted to answer this question in a randomized fashion. The results of this study are still under analysis although preliminary evaluations led to the following conclusions:

1 response by 12 weeks of therapy is an important prognostic factor;

2 etoposide plus vinblastine and steroids does not appear to confer any benefit over therapy with vinblastine and steroids;

3 prolonged therapy may decrease the reactivation rate of LCH.

In light of the risk of therapy-associated acute myelogenous leukemia/myelodysplastic syndrome in patients treated with epipodophyllotoxins (i.e., etoposide/VP-16), this study obviated the use of etoposide in LCH. This trial also confirmed that age less than 2 years without risk-organ involvement is not an independent prognostic factor. The Histiocyte Society protocol LCH-III is attempting to determine in a randomized design whether (i) intensified induction therapy, with the addition of intermediate-dose methotrexate followed by inclusion of methotrexate in maintenance therapy, improves remission induction rates and overall outcomes and (ii) whether prolonging continuation therapy reduces the rate of disease reactivation (see Fig. 15.9 for treatment

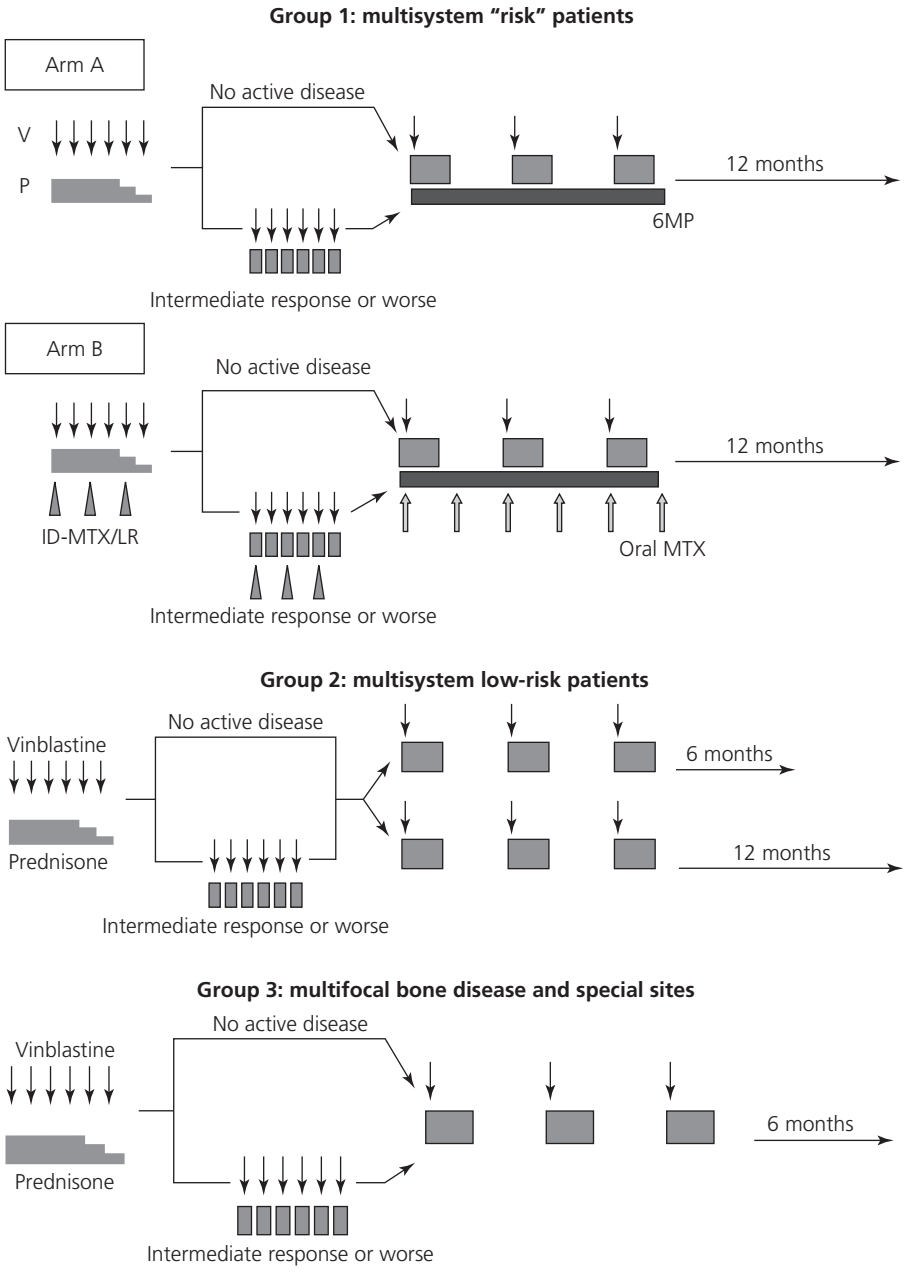

Fig. 15.9 Treatment arms for LCH-III protocol sponsored by the Histiocyte Society.

schema). Based on the results of the previous studies, etoposide is no longer recommended as initial therapy.

Despite past successes in the treatment of newly diagnosed LCH, the treatment of refractory disease remains problematic. Experience with immunosuppressive agents such as cyclosporin and antithymocyte globulin are limited and responses most commonly transient.[60] However, there is significant experience with the nucleoside analog 2-CDA, alone or in combination with cytosine arabinoside.[61–64] 2-CDA has been shown to produce a remission in more than one-third of patients with refractory disease in an international phase II study. The response rate was even better in patients with a good response to initial treatment.[38,61,63,64] 2-CDA has also shown anecdotal efficacy in the treatment of parenchymal CNS disease, although no agent has been shown to be convincingly effective in halting the progression of the neurodegenerative disease. Other approaches that have been used to treat the neurodegenerative disease associated with LCH include drugs that decrease inflammatory responses such as thalidomide and TNF inhibitors such as infliximab (Remicade) and etanercept (Enbrel).[65–67] Alemtuzumab (Campath), an anti-CD52 antibody, may also have promise in the treatment of LCH, especially in patients with advanced disease, but should be tested in prospective clinical trials because of its profound immunosuppressive effect.[68] There are case reports of hematopoietic stem cell transplantation (HSCT) in patients with refractory LCH, but the role of this therapeutic approach remains unclear in part due to difficulty in identifying matched donors and the high mortality rate in patients with significant disease-related organ dysfunction.[69] A Histiocyte Society trial is currently testing the use of a nonablative preparative regimen for HSCT.[69]

There remains a significant need for more effective agents in the treatment of patients with organ involvement and dysfunction, including those with progressive CNS, hepatic and pulmonary disease. Several new agents, including antibodies to the CD1a surface antigen as well as agents targeting cytokine receptor signaling pathways, are currently in preclinical/early clinical phases of development. It is anticipated that the optimization of these agents and their incorporation into routine clinical use will help increase our ability to more effectively treat patients with refractory and progressive disease.

Survivorship issues

Survivors of LCH can have significant late sequelae related to their disease after achieving remission and long-term cure. Late effects in survivors of LCH tend to be directly related to sites of original disease involvement. In one study, 42% of patients developed long-term complications, patients with multisystem disease being at highest risk. Diabetes insipidus developed in 15% of patients, CNS complications in 12% and pulmonary insufficiency in 10%.[41] Others have noted neurocognitive problems such as intellectual impairment, psychological problems and psychomotor retardation in long-term survivors of LCH.[49,50,70] The late CNS complications of LCH also include neurodegenerative changes that can be highly disabling.[48–50,71–73] The neurodegenerative disease is thought to be the result of a paraneoplastic process and pathologically is characterized by an inflammatory infiltrate dominated by CD8-positive reactive lymphocytes, microglial activation and gliosis. This contrasts with the T-cell infiltration and severe neurodegeneration surrounding CD1a infiltrates of CNS parenchyma.[48] Sclerosing cholangitis and liver failure necessitating liver transplant are also well recognized late effects of systemic LCH. The role of chemotherapy in the management of CNS and hepatic sequelae is limited as these complications appear to be related to an aberrant immune response and tissue fibrosis as opposed to active LCH.[74,75] Patients with LCH also have an increased risk of malignancy, which may be further increased when treated with etoposide or radiation as part of their therapy.[33,34,76]

It is critical for patients with LCH, especially multisystem disease, to be followed on a long-term basis at a center familiar with the care of patients with LCH. Follow-up should include imaging studies in addition to routine blood counts, liver and thyroid function testing as well as urine and electrolyte levels for assessment of diabetes insipidus. Formal neurocognitive evaluations should be done in patients with suspected or proven CNS involvement.

Non-Langerhans cell (class I) histiocytoses

Juvenile xanthogranulomatous disease and related disorders

The non-Langerhans cell (class I) histiocytic disorders represent a spectrum of disease defined by the accumulation of dendritic cells that do not meet the phenotypic criterion for diagnosis of LCH. These histiocytes, like LCH cells, phenotypically resemble a stage in the normal development of dendritic cells. It is believed that under growth factor stimulation, a common progenitor can develop along two separate differentiative pathways that can be phenotypically distinguished by the expression of CD14. The CD14-negative lineage, under the influence of TNF-α and GM-CSF, differentiates into Langerhans cells while the CD14-positive lineage can give rise to either cells of the monocyte–macrophage lineage or to interstitial/dermal dendrocytes.[77] Disorders arising from the monocyte–macrophage lineage are categorized as the class II or macrophage-related histiocytoses. However, the non-Langerhans cell (class I) histiocytoses are believed to arise from dermal dendritic cells. It is critical to emphasize that disorders arising from the dermal dendrocyte are now considered class I histiocytoses.

The non-Langerhans cell (class I) histiocytoses are histologically nonmalignant proliferative disorders that have variable

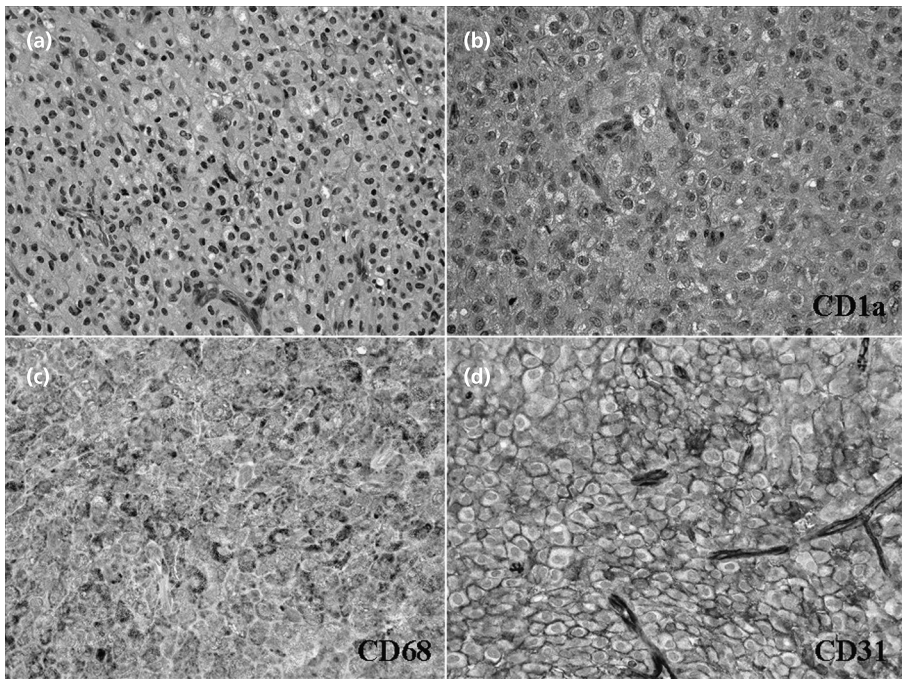

Fig. 15.10 Histopathology and immunochemical staining of juvenile xanthogranulomatous disease. (a) Juvenile xanthogranuloma characterized by oval, partially lipidized histiocytes admixed with eosinophils (hematoxylin and eosin staining) (original magnification ×200). Many juvenile xanthogranulomas also contain Touton-type multinucleated giant cells. Unlike Langerhans cell histiocytosis, juvenile xanthogranulomas do not express CD1a (b, original magnification ×400) but do express histiocyte antigens CD68 (c, original magnification ×400) and CD31 (d, original magnification ×400). Photographs courtesy of Dr John Reith, Department of Pathology, University of Florida School of Medicine, Gainesville, FL, USA.

clinical presentations. However, these disorders are all defined by the similar pathologic finding of a histiocytic proliferation that is CD1a and S100 negative but factor XIII, CD31, CD68, CD163, fascin and CD14 positive (Fig. 15.10). Clinical presentation of these disorders is variable and appears to be age dependent. It has been hypothesized that the clinical presentation of these disorders, much like LCH, depends on the variable local cytokine milieu.[78] Weitzman and Jaffe[77] have suggested that the non-Langerhans cell (class I) histiocytoses be divided into three major groups based on their clinical presentation for ease of classification: (i) disorders primarily affecting skin (cutaneous); (ii) cutaneous disorders that have a systemic component; and (iii) multisystem disorders that can also affect skin.

The juvenile xanthogranuloma (JXG) family of diseases represents the most common disorder of this subtype. Juvenile xanthogranulomatous disease is the prototypical member of this family of disorders and the most common form observed in pediatrics. The primary presentation of JXG in children is cutaneous (Fig. 15.11), although approximately 4% of children may also have systemic involvement of the CNS, liver, lungs and eyes.[79,80] JXG lesions typically self-involute, although systemic disease may sometimes necessitate chemotherapy.[77] Optimal therapy for patients with systemic JXG who need therapeutic intervention remains unclear, although LCH regimens have been most commonly used with variable responses observed.[79,81,82] Interestingly, a triple association between JXG, juvenile myelomonocytic leukemia and neurofibromatosis type I has been reported, possibly genetically linking these conditions in some patients.[83–86]

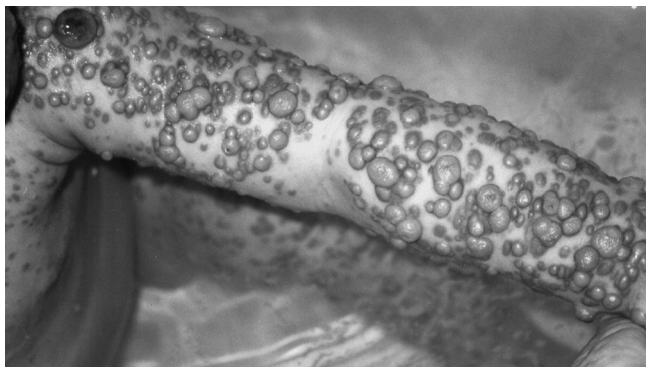

Fig. 15.11 Extensive cutaneous involvement of an infant with juvenile xanthogranulomatous disease.

Erdheim–Chester disease is also a member of the class I non-Langerhans cell histiocytoses and can often present as a systemic disease. This disease is extremely rare in the pediatric age group and patients are typically older than 50 years of age. Clinically, this disease presents with xanthoma-like skin nodules and bilateral lower extremity bone pain. Radiography shows symmetrical sclerosing bone lesions typically affecting the metaphyseal ends of long bones. Patients with disseminated disease may have severe cardiopulmonary insufficiency from parenchymal involvement of heart and lung tissues, renal insufficiency due to perinephric involvement, and CNS involvement with ataxia, diabetes insipidus and mental status changes.[87,88] This disease is frequently progressive and fatal. Limited success has been reported when treating patients with Erdheim–Chester disease with standard LCH therapy, although anecdotal

cases of response to low-dose IFN-α are notable but in need of prospective confirmation.[91]

Disorders of varied biological behavior: macrophage-related (class II) histiocytoses

Hemophagocytic lymphohistiocytosis

Biology

Class II histiocytic disorders are all characterized by the abnormal accumulation of activated macrophages along with lymphocytes in tissues. The predominant member of the class II histiocytoses is hemophagocytic lymphohistiocytosis (HLH), a disorder characterized by the abnormal accumulation of T lymphocytes and macrophages in normal tissues. HLH is further subdivided as follows:

1 primary HLH (familial erythrophagocytic lymphohistiocytosis), a heritable autosomal recessive disorder;

2 secondary HLH, a sporadic disease typically associated with a preexisting inflammatory condition such as infection (infection-associated hemophagocytic syndrome), malignancy (malignancy-associated hemophagocytic syndrome) or immunosuppressive therapy (macrophage activation syndrome).

Primary and secondary HLH are clinically indistinguishable. The presentation of these disorders is typically fulminant and consists of fever, cytopenias, hepatosplenomegaly, hyperbilirubinemia, hyperlipidemia, hypofibrinogenemia, coagulopathy, hemophagocytosis and CNS abnormalities such as seizures.[90,91] A family history of consanguinity and age < 2 years at time of onset are highly suggestive of primary/inherited HLH. Positive genetic testing for genes known to cause HLH establishes the diagnosis of the primary or inherited form of the disease.

The immunologic defect underlying primary HLH is low or absent natural killer (NK) cell and cytotoxic T-lymphocyte function and number.[92,95] This diminished cytotoxic function is responsible for the pathologic expansion of cellular immune responses and infiltration of tissues by inflammatory cells. This accumulation of activated macrophages and lymphocytes in tissues is perpetuated by the release of inflammatory cytokines by both lymphocytes and antigen-presenting cells, resulting in systemic hypercytokinemia which in turn contributes to organ damage and the signs and symptoms of HLH.[96–98]

Mutations in three genes have now been identified in patients with primary HLH: *PRF1* (perforin),[99] *UNC13-D* (Munc13-4)[100] and *STX11* (syntaxin 11).[99–101] Perforin is stored in cytotoxic granules of NK cells and cytotoxic T cells and is released to the cell surface during the formation of an immunologic synapse, where it functions to create pores in the cytoplasmic membranes of target cells leading to cell death. Munc13-4 and syntaxin 11 are both involved in the stabilization and transport of cytotoxic granules in NK and T cells. Normal NK-cell and T-cell function is crucial in the clearance of infections, particularly viral infections through lysis of infected cells.[102,103] The association of *PRF1*, *UNC13-D* and *STX11* mutations with HLH and the observed NK-cell defects in patients with HLH clearly point to the central role of this pathway in the pathogenesis of HLH. Furthermore, *in vitro* NK-cell enumeration and cytotoxicity data suggest significant variability among patients with HLH that is directly related to the nature of their genetic defect.[104]

This pathophysiologic model for HLH is further supported by the reports of HLH-like syndromes in patients with other immunodeficiency diseases such as Chédiak–Higashi syndrome (*LYST*), Griscelli syndrome (*RAB27A*) and X-linked lymphoproliferative syndrome (*SH2D1A*).[105–107] Mutations in the perforin gene are thought to account for 20–58% of cases of primary HLH (Table 15.3) [101, 110–112]. Interestingly, patients with HLH with missense mutations and higher levels of perforin expression appear to have a delayed onset of symptoms relative to patients with no expression of perforin.[111]

Incidence and epidemiology

The incidence of primary HLH is estimated to be around 1 in 50 000–300 000 live births based on several retrospective epidemiologic studies.[112–114] However, these estimations may

Table 15.3 Genetic defects in primary and secondary hemophagocytic lymphohistiocytosis.

Disease	Associated gene	Gene function	Chromosomal location
FHLH-1	Unknown	Unknown	9q21.3–q22
FHLH-2	*PRF1*	Induction of apoptosis	10q21–q22
FHLH-3	*UNC13-D*	Vesicle priming	17q25
FHLH-4	*STX11*	Vesicle transport; t-SNARE	6q24
GS-2	*RAB27A*	Vesicle transport; small GTPase	15q21
CHS-1	*LYST*	Vesicle transport; not further defined	1q42.1–q42.2
XLP	*SH2D1A*	Signal transduction and activation of lymphocytes	Xq25

CHS, Chédiak–Higashi syndrome; FHLH, familial hemophagocytic lymphohistiocytosis; GS, Griscelli syndrome; XLP, X-linked lymphoproliferative syndrome.
Adapted with permission from Janka G, zur Stadt U. *Hematology (Am Soc Hematol Educ Program)* 2005; 82–8.

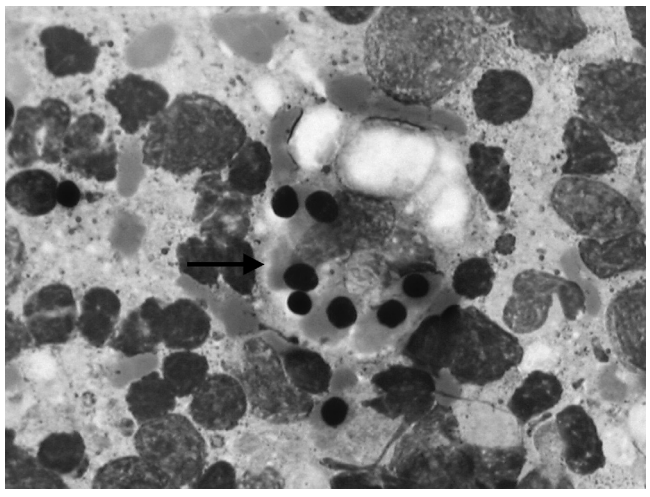

Fig. 15.12 Bone marrow biopsy from an infant presenting with pancytopenia, fever and hepatic failure shows evidence of large macrophages phagocytosing a white cell and multiple red cells (arrow). Courtesy of Dr Ying Li, Department of Pathology, University of Florida School of Medicine, Gainesville, FL, USA.

under estimate the true incidence of HLH secondary to lack of familiarity of many primary physicians with this diagnosis. Interestingly, the prevalence of primary HLH is noted to be geographic in distribution, a finding attributed to the familial nature and the founder effect seen in this disease.[113,115,116]

The majority of cases of primary HLH occur within the first year of life, although cases have been reported as late as the third decade of life.[117,118] Secondary HLH, however, occurs sporadically and can be seen at any age depending on the primary initiating event. The male to female ratio of primary HLH is estimated to be 1 : 1, with some studies suggesting a slight male predominance.[113,117,118]

Clinical presentation

HLH is fatal if the diagnosis is delayed and appropriate therapy not instituted rapidly. The most common presenting symptoms include fever and hepatosplenomegaly, although rash, lymphadenopathy and CNS symptoms are common. Signs and symptoms also include cytopenias, transaminitis, coagulopathy, hypofibrinogenemia, hypertriglyceridemia, hyperferritinemia, and evidence of hemophagocytosis from bone marrow aspiration (Fig. 15.12). As significant variability in clinical presentation may impede diagnosis, specific diagnostic criteria have been established by the Histiocyte Society to aid in more expeditious diagnosis and treatment (Table 15.4).[41] In particular, some children may present with solely or primarily CNS-related symptoms; in these children a high level of suspicion on observing characteristic brain MRI changes is important in making an early diagnosis. If strong clinical suspicion is present, it is recommended that therapy be initiated even if all criteria are not fully satisfied.

Table 15.4 Diagnostic criteria for hemophagocytic lymphohistiocytosis.*

Clinical
Fever
Hepatosplenomegaly
Laboratory
Hematologic
Cytopenias (more than two of three lineages in peripheral blood)
Hemophagocytosis
Biochemical
Hypertriglyceridemia (fasting triglycerides ≥ 2 mmol/L or ≥ 3SD above normal)
Hypofibrinogenemia (≤ 1.5 g/L or ≤ 3SD below normal)
Hyperferritinemia
Immunologic
Low or absent natural killer cell function
Elevated soluble CD25 serum levels
Additional
Molecular demonstration of known gene mutation
Presence of familial disease

* Diagnosis requires five of the eight clinical and laboratory criteria or the identification of specific gene mutations or presence of familial disease.

In such cases, bone marrow studies should be repeated if initially negative to help establish a diagnosis by documenting hemophagocytosis. The presence of a family history positive for consanguinity or another affected sibling as well as the availability of molecular testing for gene mutations can further assist in establishing a diagnosis.

Treatment

Current therapy of HLH, as prescribed by the HLH-2004 protocol of the Histiocyte Society, consists of dexamethasone, etoposide and cyclosporin in combination with intrathecal methotrexate and prednisolone when indicated by the presence of cerebrospinal fluid pleocytosis. Antithymocyte globulin has also been used, but mostly as second-line therapy.[119] Primary HLH tends to be recurrent and does not permanently respond to chemotherapy, thus necessitating HSCT for cure.[66,120,121] However, secondary HLH, with the exception of refractory cases, can often be effectively treated with chemotherapy or immunomodulatory approaches such as intravenous immunoglobulin.[122–126] Treatment of an underlying infection or malignancy, while necessary, may be inadequate in cases of secondary HLH, necessitating HLH-type therapy. Thus, in cases of infection-associated or malignancy-associated HLH, there is often a need to sequentially treat both the HLH and the underlying disorder in order to achieve complete remission. HSCT is usually necessary in patients with recurrent secondary HLH.

The current Histiocyle Society international study, HLH-2004, is based on the HLH-94 study. The HLH-94 protocol

achieved an estimated survival rate of 55% at a median of about 3 years of follow-up. This rate was slightly lower in patients with familial HLH (51%), although patients who underwent bone marrow transplantation had a 3-year survival probability of 62%. As a significant number of patients on HLH-94 died prior to receiving bone marrow transplantation, the HLH-2004 protocol has been modified so that cyclosporin is administered concurrently with dexamethasone and etoposide at the beginning of therapy with the goal of improving on the early treatment failure rate.[66]

Survivorship issues

The primary long-term sequelae of HLH are mainly related to the extent of CNS involvement. Prompt initiation of systemic therapy is critical for reducing CNS morbidity in HLH. Although the benefits of intrathecal therapy have not been clinically proven, inclusion of intrathecal therapy in patients with documented CNS disease is recommended.[91,127–129] Close follow-up of neurologic function is critical in order to assess the developmental delay that has been observed in these patients. It remains unclear if the neurologic complications are a direct result of disease involvement, therapy or infectious complications.[130] Long-term follow-up is a critical part of the care of HLH patients and should include observation for CNS effects, bone marrow transplant-related morbidities, and secondary acute myeloid leukemia related to the use of etoposide.[131]

Sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease)

Other members of the class II histiocytoses tend to have a more indolent course than HLH. Sinus histiocytosis with massive lymphadenopathy (SHML), also known as Rosai–Dorfman disease, is characterized by a lymphohistiocytic accumulation in the sinuses of lymph nodes without architectural effacement.[132] The proliferative macrophages seen in this disorder are typically S100 positive but CD1a negative and can be characteristically observed to wrap around intact lymphocytes or other cells, a process known as emperipolesis. SHML has a predilection for lymph nodes of the head and neck but can be seen in any organ including the CNS.[133–137] SHML more commonly occurs in patients of African ancestry; and is not typically responsive to most therapeutic approaches.[138] Recent reports have documented response to therapy with high-dose dexamethasone and also with 2-CDA.[133,139,140] Although SHML can be potentially disfiguring, it is only rarely life-threatening.

Malignant (class III) histiocytoses

This class of disorders consists of malignant histiocytosis, histiocytic sarcoma and acute monocytic leukemia. For the most part, these disorders can be characterized by malignant transformation of cells of the MPS with significant cellular atypia. Those disorders characterized by malignant transformation of dendritic cells are often treated with lymphoma/leukemia protocols, including HSCT, although outcomes remain relatively poor. The wide variety of these conditions, the rarity of occurrence in pediatrics, and discussion elsewhere in this book (see Chapter 16) preclude a more detailed discussion here.

Challenges

Important landmarks have been achieved in our understanding of LCH since the first descriptions from the 1800s. We have a better understanding of the normal and abnormal responses of cells belonging to the MPS as well as of the etiology, presentation, natural history and treatment of LCH. Nevertheless, large numbers of patients remain undiagnosed or inadequately treated or simply do not respond to current therapies. The outcome for patients with LCH, particularly with refractory disease or disease involving organs such as the bone marrow, liver, lung and CNS, remains poor. The cure rate of HLH still remains close to 50%, with many survivors having significant adverse long-term sequelae. The formation of the Histiocyte Society has helped establish a framework within which collaborative studies can be undertaken. Future efforts should focus on further defining the etiology of LCH and understanding the molecular pathways with the goal of identifying molecular targets for more effective treatment and improved outcomes. Additionally, improved clinical understanding of the natural history of the histiocytoses is an important key to early diagnosis and appropriate therapy. Cooperative group clinical trials involving multidisciplinary approaches, particularly involving medical and pediatric oncologists, should help establish future improvements in outcome for patients with histiocytosis.

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