Chapter 17
Langerhans Cell Histiocytosis

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17.1 Introduction

Langerhans cell histiocytosis refers to a rare group of diseases that derive from a clonal proliferation and accumulation of Langerhans cells (1). The latter are specialized antigen-presenting cells of dendritic origin present at the dermal/epidermal border of the skin and as a meshwork throughout the epidermis. The Histiocyte Society, an international network of European, North and South American, and Asian groups that conduct cooperative studies of the histiocytoses, has divided histiocytic diseases into three groups: Langerhans cell histiocytosis (class I), non-Langerhans cell histiocytoses (class II), and malignant histiocytoses (class III) (2, 3). Langerhans cell histiocytosis, historically known as histiocytosis X, eosinophilic granuloma, or Langerhans cell granulomatosis, encompasses many different clinical manifestations. The Histiocyte Society classifies Langerhans cell histiocytosis according to the number of sites and types of tissue/organ involved and the presence or absence of involved organ failure. Historically, the disease comprises three main and sometimes overlapping clinical syndromes: unifocal disease (solitary eosinophilic granuloma), multifocal unisystem disease (including cases of Hand-Schüller-Christian syndrome), and multifocal multisystem disease (including cases of Letterer-Siwe syndrome) (1; 4–6). Langerhans cell histiocytosis also encompasses some cases belonging to syndromes previously described as reticuloendotheliosis, Hashimoto-Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, Type II histiocytosis, and nonlipid reticuloendotheliosis.

17.2 Epidemiology

Langerhans cell histiocytosis is an extremely rare disease that affects approximately five in a million children and approaches one in a million adults (2, 4, 7–9). Approximately 1200 new cases are reported annually in the United States. These figures may be spuriously low because of the failure to diagnose and report cases with a mild course or spontaneous healing of isolated lesions (10). Males are

S.M. Ansell (ed.), *Rare Hematological Malignancies.*

affected twice as often as females. Patients of northern European descent are more frequently afflicted than patients of Hispanic heritage, and the disease has only rarely been described in patients of African ancestry (11–13). The age at presentation varies with the clinical syndrome, but the disease occurs primarily in the pediatric population. Langerhans cell histiocytosis involving a solitary site (other than the lung) is found predominantly in older children (4, 8, 13). The age of presentation with multifocal unisystem disease is approximately 2–10 years. The median age of presentation with multifocal multisystem disease is less than 3 years (4, 7, 8). Solitary lung involvement is a unique clinical manifestation of Langerhans cell histiocytosis and usually occurs in young adults between 20 and 40 years of age, with a slight female predominance (4, 14). However, all of the clinical syndromes have been reported in all age groups. Early reports describe sibships and kindreds who had what appears to be Letterer-Siwe disease. Although many of the earlier reports were actually describing non-Langerhans cell histiocytosis reticulohistiocytic disorders, rare well-documented cases of Langerhans cell histiocytosis have appeared in families (15–17).

17.3 Etiology

The etiology of the disease is unknown, but the abnormal cells of Langerhans cell histiocytosis from bone/chronic lesions have been shown to be immature Langerhans-type dendritic cells, thought to arise from blockage in the normal maturational pathway of Langerhans cells (2, 18, 19). However, whether Langerhans cell histiocytosis is a neoplastic, immunodysregulatory, or reactive disorder has been the subject of considerable debate. Many observations favor a reactive etiology, including the bland cytologic features of the Langerhans cells, the presence of numerous inflammatory cells (including granulomalike lesions), reports of spontaneous remissions, inability of Langerhans cell histiocytosis tissue samples to establish cell lines, and patterns of disease spread in individual patients (19). However, evidence in favor of a Langerhans cell histiocytosis being a neoplastic process includes the infiltrative nature of the atypical cells, the occurrence of bona fide familial cases, and the patterns of X-chromosome inactivation in the X-linked human androgen-receptor gene, which demonstrate that Langerhans cell histiocytosis is a monoclonal proliferation (17, 20, 21). Similar studies using X-linked polymorphic DNA probes have not found clonality in the T-lymphocytes of Langerhans cell histiocytosis. Except for rare reports of HHV6- and Epstein-Barr virus (EBV)-associated cases, most investigators have not found molecular evidence of a viral etiology (22–24). Comparative genomic hybridization, conventional cytogenetics, and loss of heterozygosity analyses have shown some mutational events in Langerhans cells histiocytosis, particularly involving chromosomes 1p and 7 (25–27). Interestingly, some early reports of Langerhans cell histiocytosis concurrent with myelodysplasia in children also involved chromosomes 7 and 1 (28). In fact, certain patients with myelodysplasia or acute myeloid leukemia with monosomy 7 have been reported

to develop diabetes insipidus, a common feature of some forms of Langerhans cell histiocytosis (29, 30).

Isolated Langerhans cell histiocytosis of the lung is the only form of the disease known to be associated with an environmental risk factor, namely cigarette smoking. Cessation of smoking often results in tumor regression (14, 31). Lesions from these patients have been found to be nonclonal by HUMARA assay (32) Many investigators consider isolated pulmonary Langerhans cell histiocytosis associated with smoking to be a different disease process from the other forms of Langerhans cell histiocytosis, including those that might involve the lung as part of multisystem involvement.

Malignant diseases such as carcinoma, lymphoma, and leukemia have long been associated with Langerhans cell histiocytosis and may precede, follow, or occur at the same time (33). A focus of Langerhans cell histiocytosis may be seen adjacent to a hematopoietic malignancy, which may include non-Hodgkin or Hodgkin lymphomas, or leukemia (usually acute nonlymphocytic leukemia) (33–36). In cases associated with non-Hodgkin lymphoma, the Langerhans cell histiocytosis lesion is usually small and concurrent, but rarely, Langerhans cell histiocytosis has subsequently developed at other sites in these patients (35, 37). In contrast, in cases of Langerhans cell histiocytosis associated with leukemia, the Langerhans cell histiocytosis typically precedes the diagnosis of malignancy (33, 35). Langerhans cell histiocytosis has also been described in association with a variety of solid tumors. Cigarette smoking is the most likely etiology for the high prevalence of pulmonary and extrapulmonary malignancies in patients with pulmonary Langerhans cell histiocytosis (37) Most cases of malignancy follow Langerhans cell histiocytosis therapy and one cannot state with certainty whether such cases are due to individual predisposition to tumor development, with or without the contribution of potentially mutagenic Langerhans cell histiocytosis therapy.

Immune dysfunction most likely plays a large role in the pathogenesis of Langerhans cell histiocytosis. One hypothesis is that Langerhans cell histiocytosis development may be due to a failure to switch from the innate to adaptive immune response (38). Most investigators accept that the innate immune response in Langerhans cell histiocytosis patients is defective, but no specific immune system defect has been identified. However, there do appear to be defects in interactions between T-cells and macrophages, as well as between T-cells and Langerhans cells, which might result in a cytokine amplification cascade both locally and systemically (39). This cytokine "storm" may explain some of the clinical features of Langerhans cell histiocytosis such as fibrosis, necrosis, osteolysis, wasting, and fever. The cells of Langerhans cell histiocytosis are considered immature and unable to present antigens effectively, which is the usual role of normal Langerhans cells. Rather than an intrinsic defect, this is thought to be heavily influenced by the microenvironment, namely the production of numerous cytokines by the different types of cells, including non-Langerhans cells such as macrophages (18). A possible mechanism for the accumulation of defective Langerhans cells in lesions is related to chemokines of the cell surface. The Langerhans cell histiocytosis cells may aberrantly express chemokines of immature dendritic cells (40). This abnormal expression might help

contribute to homing to lymphoid and nonlymphoid organs and might recruit eosinophils and CD4+ T-cells, both of which secrete more cytokines that influence the Langerhans cell histiocytosis cells to remain in an immature state.

17.4 Clinical Features

Langerhans cell histiocytosis is currently classified into localized and disseminated disease, as listed in Table 17.1 (2, 41). Localized disease, a form of "single-system disease," usually includes a single lesion in the bone, skin, or lymph node. As previously discussed, isolated pulmonary involvement probably represents a different disease entity. "Single-system disease" may also involve multiple sites within the same organ system, such as multiple lesions in one bone, multiple lesions in two or more different bones, multiple lymph node involvement, or multiple skin lesions. Lesions that have a tendency to involve the nervous system, usually by direct extension, include those involving the facial bones, sinuses, maxilla, or anterior or middle cranial fossa. These forms of "single-system disease" account for approximately one-third of patients (8). The other two-thirds of patients have a disseminated or multisystemic form of Langerhans cell histiocytosis, which is further divided into two categories ("low risk" and "high risk"), according to clinical course and response to treatment (42). The "risk organs" include the hematopoietic system, lungs, liver, or spleen. The low-risk group comprises patients with Langerhans cell histiocytosis lesions in multiple organs, but not involving the risk organs. The high-risk group comprises patients whose Langerhans cell histiocytosis lesions involve

Table 17.1 Classification of Langerhans cell histiocytosis

Single system disease	
Localized (single site)	Monostotic bone involvement
	Isolated skin involvement
	Solitary lymph node involvement
Multiple site	Polyostotic bone involvement
	Multifocal bone lesions (in two or more different bones)
	Multiple skin lesions
	Multiple lymph node involvement
Multisystem disease	
Low-risk group	Disseminated disease (≥2 organs involved), without involvement of lymph nodes, bone marrow, spleen, lungs, or liver
High-risk group	Disseminated disease (≥2 organs involved), with involvement of lymph nodes, bone marrow, spleen, lungs, or liver
CNS risk lesions	
	Involvement of facial bones, sinuses, maxilla, or anterior or middle cranial fossa (temporal, mastoid, sphenoidal, ethmoidal, zygomatic, orbital bones) with intracranial tumor extension

Source: Adapted from Ref. 41.

multiple organs, with involvement of one or more of the risk organs. Thus, adults with solitary pulmonary involvement would not be considered to have a high-risk lesion, despite involvement of lung.

The clinical presentation of Langerhans cell histiocytosis depends on the extent of dissemination (4, 8, 27, 43). The most common site of presentation of single site (or unifocal unisystem) disease is the bone. Single site bony disease may be asymptomatic and the incidental finding in the workup of an unrelated disorder. However, pain and tender swelling are common symptoms. The radiograph shows a single, sharply demarcated osteolytic lesion. Patients with single system, multiple site (or multifocal unisystem) disease may have bony defects with exophthalmos (usually due to tumor infiltration of the orbital cavity and the orbital bones), diabetes insipidus (due to involvement of the sella turcica with invasion of the pituitary gland), and loss of teeth (due to mandibular involvement and gum infiltration). Regardless of whether the disease is solitary or multiple, bony lesions usually are found in the long or flat bones: in children, the calvaria and the femur, and in adults, the skull or ribs. The mandible, scapula, ilium, and the anterior portion of the vertebral bodies of the lumbosacral vertebrae may also be affected in both the unifocal and multifocal variants of bony Langerhans cell histiocytosis (3, 4). The bones of the hands, wrists, knees, feet, and cervical vertebrae are uncommonly affected. Spontaneous fractures might result from the Langerhans cell histiocytosis lesions in the long bones, and vertebral collapse may result in spinal cord compression. Neurologic symptoms may occur if the skull lesion extends into the nervous system. Likewise, when Langerhans cell histiocytosis involves the temporal or mastoid bones, purulent external otitis media is common. Diabetes insipidus affects 25–40% of patients who present with unisystemic bone Langerhans cell histiocytosis and involvement of the skull (41, 43, 44). The diabetes insipidus may worsen in patients with Langerhans cell histiocytosis who are pregnant (45). Hypothalamic infiltration and pancreatic and thyroid involvement may result in hyperprolactinemia and hypogonadism (46). Single system Langerhans cell histiocytosis may also present in the skin as noduloulcerative lesions in the oral, perineal, perivulvar, or retroauricular regions. Skin lesions may also manifest as extensive coalescing, scaling, or crusted papules. One-third of patients with the classic multifocal single system form of Langerhans cell histiocytosis have skin mucocutaneous lesions that might present as described earlier, with nodular infiltrates and ulcerated plaques in the mouth, axillae, or anogenital region (47). Patients with lymph node involvement (usually cervical or inguinal region) are usually afebrile but may have painful lymphadenopathy (48). Lymphadenopathy and skin rashes due to Langerhans cell histiocytosis have been reported to transiently regress during pregnancy (49). Other reported sites of isolated disease include the thymus and soft tissue.

Patients with isolated lung involvement usually present with cough, dyspnea, chest pain, fever, hemoptysis, or weight loss. Approximately 20% of patients are asymptomatic (50). The chest radiograph varies from a micronodular and interstitial pattern in the early stages to a “honeycomb lung” appearance (50, 51). Depending on the stage of the lesions, high-resolution computed tomography (CT) scan of the chest shows nodules to cavitated nodules and thick-walled cysts to cysts to confluent cysts (52).

Multisystem disease is the rarest (10% of all cases) and most aggressive form of Langerhans cell histiocytosis and generally involves the skin, lymph nodes, lung, and liver (4, 43). Symptoms include anorexia, failure to thrive, fever, and pulmonary lesions/symptoms, such as cough, dyspnea, tachypnea, hemoptysis, chest pain, and pneumothorax. Chronic otitis media, lymphadenopathy, and hepatosplenomegaly are also common. Skin involvement is present in almost 80% of patients and may be the first sign of disease (47). They usually manifest as a generalized erythematous or weeping eczematoid rash extensively affecting the scalp, ear canals, abdomen, buttocks, intertriginous areas, and face. Ulcerated and denuded skin may serve as a portal for microorganisms and may lead to sepsis. Osteolytic lesions are not common in the multifocal multisystemic form of Langerhans cell histiocytosis, but the mastoid may be affected, resulting in otitis media. Aural discharge, conductive hearing loss, and postauricular swelling have been described. Lung involvement may result in diminished oxygen diffusion and lung capacity. Laboratory abnormalities include anemia in the absence of iron deficiency or significant infection, leukopenia, neutropenia, or thrombocytopenia.

The workup of a patient suspected of having Langerhans cell histiocytosis should include a complete blood cell count (CBC) with differential, a reticulocyte count, an erythrocyte sedimentation rate, a direct and indirect Coombs test, and immunoglobulin levels (2). If the CBC reveals any cytopenia, a bone marrow study should be performed (53). Coagulation studies may be useful. Other laboratory tests may include liver function tests, which, if abnormal, should prompt a liver biopsy, and urine osmolarity, to screen for diabetes insipidus. Imaging studies should include chest radiographs, a skeletal radiograph survey, and CT scan or magnetic resonance imaging (MRI) scans of the hypothalamic–pituitary region. Patients with radiographic evidence of pulmonary involvement, in whom chemotherapy is being considered, should undergo a bronchoalveolar lavage (and biopsy if necessary) to exclude opportunistic infections. Pulmonary function testing may show reduced carbon monoxide diffusing capacity of the lungs in 70–90% of cases (54).

Depending on the clinical situation, workup should also include a small bowel series and biopsy (for cases of unexplained diarrhea, failure to thrive, and malabsorption), hormonal studies (to investigate the hypothalamic–pituitary axis), and visual or neurologic testing. Skin biopsy, lymph node biopsy, or bone marrow or liver biopsy procedures may be warranted.

17.5 Diagnosis and Pathology

The diagnosis of Langerhans cell histiocytosis is made by biopsy of the affected organ. In general, the microscopic features do not allow distinction between the disseminated and localized forms of Langerhans cell histiocytosis. Langerhans cell histiocytosis may affect a portion of the biopsied tissue or might totally replace any normal anatomic structures. Despite the variation in the site, size, and architecture of Langerhans cell histiocytosis lesions, one always sees a proliferation of

pathognomonic Langerhans cells in the appropriate cellular milieu. In fact, it is the histologic picture of these unique cells that unifies the protean clinical presentations of Langerhans cell histiocytosis (Figure 17.1) (2, 4).

Normal Langerhans cells are mononuclear cells, approximately 12–15 μm in diameter, with a moderate amount of eosinophilic cytoplasm, and are usually found in the basal layer of the epidermis. The cells of Langerhans cell histiocytosis may be slightly larger, but like their normal counterpart, they usually contain an irregularly shaped nucleus, which may be folded, grooved, or lobulated. Nucleoli are usually inconspicuous. Slight cytologic atypia may be observed. The nuclear membrane is thin, and the chromatin is finely dispersed or vacuolated. In addition to the Langerhans cells, Langerhans cell histiocytosis lesions contain variable numbers of reactive cells, including eosinophils, histiocytes, neutrophils, and small lymphocytes. Eosinophilic microabscesses and granulomas are often seen. Plasma cells usually are not seen. The number of mitoses varies widely from lesion to lesion (4). Bony lesions may contain more necrosis, eosinophils, and multinucleated histiocytes than lesions found in the skin, lung, or lymph node (4, 55). As lesions age, they tend to have more histiocytes and fibrosis and fewer Langerhans cells and eosinophils (55, 56). In very late lesions, fibrosis is markedly increased and the cellular composition may predominantly be foamy histiocytes, lymphocytes and plasma cells, with only rare Langerhans cells.

The Langerhans cells are not morphologically distinctive; thus, ancillary studies are necessary. In fact, Birbeck granules by ultrastructural examination and/or CD1a positivity by immunohistochemistry are required for a definitive diagnosis of

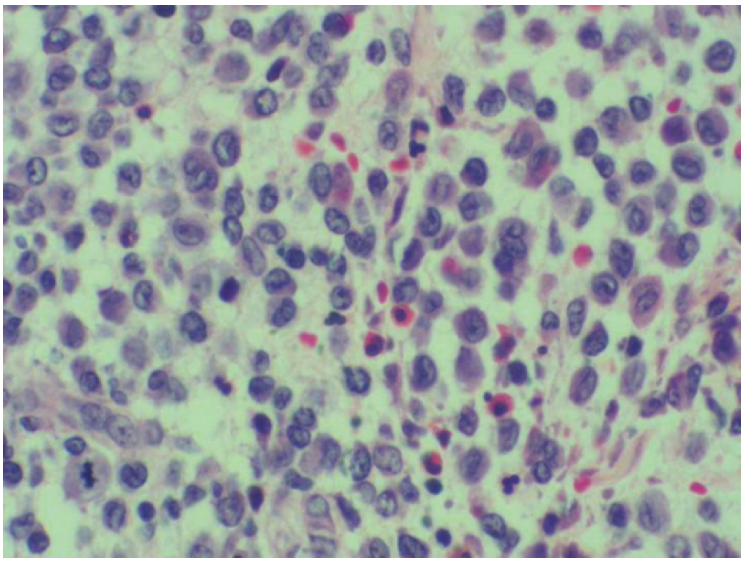

Figure 17.1 Langerhans cell histiocytosis. Langerhans cells, with their characteristic grooved nuclei, are seen admixed with eosinophils and plasma cells

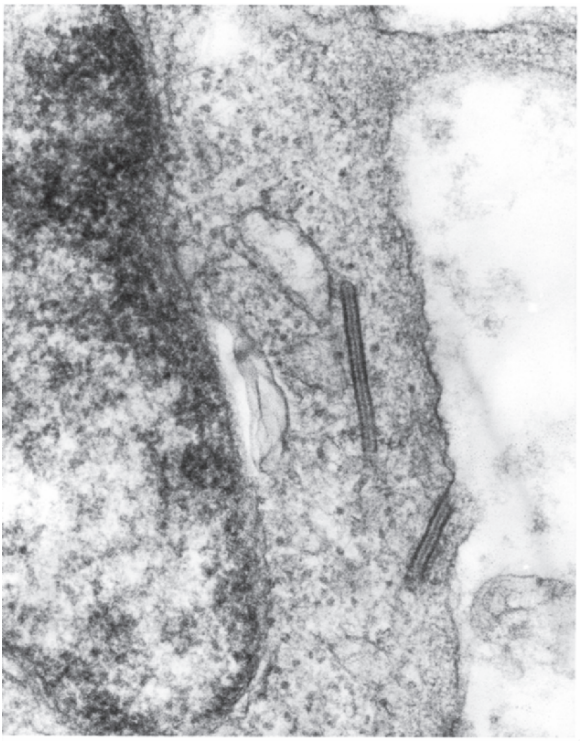

Figure 17.2 Electron micrograph of a Birbeck granule shows two rods, which are 33 nm in diameter, each with a central zipperlike striation. (Courtesy of Dr. Stephen Romansky, Long Beach, CA)

Langerhans cell histiocytosis (2). Ultrastructural examination shows that the cells have numerous lysosomes, small vesicles, multivesicular bodies, and irregular plasma membranes, and the absence of cell junctions, microvilli, desmosomes, tonofilaments, and melanosomes. The Birbeck granule, a pentilaminar "tennis-racket"-shaped intracytoplasmic membranous body with a zipperlike "handle," has remained for years the ultrastructural hallmark of Langerhans cell histiocytosis (Figure 17.2) (57). Formation of Birbeck granules are thought to be induced by a surface protein, which investigators have termed "langerin" (58). Birbeck granules are about 200–400 nm in length and about 33 nm in width, with an osmiophilic core and a double outer sheath. These unique granules are very fragile and are often destroyed in routine processing. Thus, although they are theoretically present in every Langerhans cell histiocytosis lesion, the percentage of cells containing the pathognomonic granules varies from case to case (4, 55).

Paraffin section immunohistochemical studies of Langerhans cell histiocytosis show that the Langerhans cells always express CD1a (Figure 17.3) and almost always express S100 protein (Figure 17.4) (4, 41, 43). The expression of CD1a is virtually pathognomonic and has been accepted as the strongest positive indicator

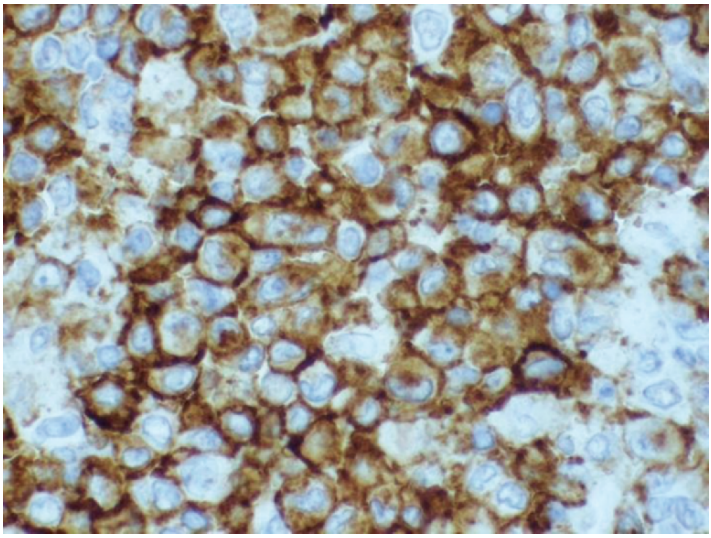

Figure 17.3 Langerhans cell histiocytosis. CD1a immunohistochemistry shows crisp membrane staining of Langerhans cells

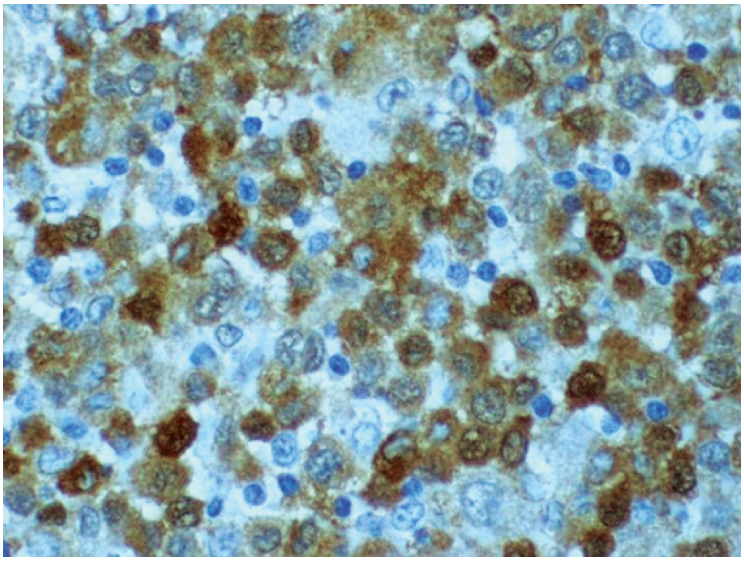

Figure 17.4 Langerhans cell histiocytosis. S100 immunohistochemistry shows variable intensity nuclear and cytoplasmic staining of Langerhans cells

of a Langerhans cell histiocytosis diagnosis, with the exception of Birbeck granules. Other histiocytic and dendritic cells do not express CD1a. In fact, CD1a expression is limited to reactive and lesional Langerhans cells, immature thymocytes, and T-lymphoblastic neoplasms. Langerhans cells also frequently express langerin, peanut agglutinin lectin, vimentin, CD74, the Fc receptor, and HLA-DR, as well as cytoplasmic CD2 and CD3 (59, 60). CD68 and antiplacental alkaline phosphatase may show a granular cytoplasmic pattern of variable intensity in a fraction of Langerhans cell histiocytosis cells (61). They are variably positive for CD45 and lysosome. They do not express CD163, CD35, CD30, CD34, or most B- and T-cell lineage markers (60, 62). The histiocytes, foamy histiocytes, and multinucleated cells often found in the lesions of Langerhans cell histiocytosis mark as ordinary nonneoplastic histiocytes and do not possess the antigenic characteristics of Langerhans cells.

Molecular hybridization studies show a germline configuration for the immunoglobulin heavy chain and α-, β-, and γ-T-cell receptor genes (21, 63). The enzyme histochemical profile of Langerhans cell histiocytosis cells is similar to normal Langerhans cells and other antigen-presenting cells in that they have low levels of lysosomal enzymes, have ATPase activity, and do not have peroxidase activity (64). They strongly express Class II histocompatability proteins and HLA-DR antigen, and they have receptor sites for the Fc portion of the IgG molecule and the third component of complement (18).

17.6 Differential Diagnosis

The clinical differential diagnosis of Langerhans cell histiocytosis includes the seborrheic dermatitides, Wiskott-Aldrich syndrome, mastocytosis, congenital candidiasis, neonatal varicella, and perianal herpes simplex. The patient's age, clinical course, laboratory and microbiology studies, and radiographic films will lead most astute clinicians to obtain a biopsy. However, because the presenting symptoms of Langerhans cell histiocytosis are nonspecific, particularly in single site involvement, the diagnosis is often delayed by a few to several months (44).

The microscopic differential diagnosis of Langerhans cell histiocytosis is quite varied and depends on the site of involvement. As previously stated, the identification of Birbeck granules or the presence of CD1a positivity in the Langerhans cells of Langerhans cell histiocytosis is specific, with the caveat that pertinent negative markers are also examined (2). However, prior to ordering these ancillary studies, the pure histologic differential diagnosis of Langerhans cell histiocytosis may include, in lymph nodes, reactive sinusoidal hyperplasia or dermatopathic lymphadenitis, or, in any other biopsied site, sinus histiocytosis with massive lymphadenopathy, metastatic neoplasms, and sinusoidal malignant lymphoma. In these cases, the distinctive ultrastructural and immunohistochemical profile that characterize the Langerhans cells of Langerhans cell histiocytosis can distinguish it from the other benign and malignant lesions.

17.7 Treatment

In the past, the multifaceted clinical presentations of Langerhans cell histiocytosis seemed to demand a unique approach to the therapy of each patient. Fortunately, data from international cooperative studies of childhood Langerhans cell histiocytosis have been very helpful in assessing the response to therapy, as well as elucidating the clinical features and underlying nature of the disease as previously described (2, 9, 19, 41, 43, 65). The different treatment options for Langerhans cell histiocytosis include watchful waiting, local treatment, immunomodulation, irradiation, chemotherapy, and liver, lung, and allogeneic hematopoietic cell transplantation.

When Langerhans cell histiocytosis is limited to a single skull lesion in the frontal, parietal, and occipital areas or a solitary lesion in a skeletal bone, watchful waiting, surgical curettage, excision, or resection might be sufficient. Painful bone lesions may require intralesional steroid injection. Polyostotic bone lesions may be treated with vinblastine or a short course of systemic steroids. Localized skin disease may be treated with a moderate to potent topical steroid or surgery. Topical nitrogen mustard (20% solution) may be needed for severe cutaneous involvement. PUVA (psoralen plus ultraviolet A) is an excellent treatment for solitary cutaneous disease. Regional lymph node enlargement can be resected or treated with a short course of systemic steroids. Involvement of the jaw bones requires a 6-month course of vincristine and prednisone.

The first clinical trials for Langerhans cell histiocytosis (LCH-I and LCH-II) by the Histiocyte Society were opened for children in the 1990s and resulted in three important observations (19, 42, 66). First, radiation or single-drug administration is not sufficient for patients with multiple bone lesions. Second, etoposide as a treatment agent did not have any additional therapeutic benefit when examining response, survival, or reactivation frequency, either as a single agent or in combination with vinblastine and prednisone. Because of the link between etoposide and an increased risk of therapy-related myelodysplasia or acute myeloid leukemia, vinblastine has remained the preferred treatment for Langerhans cell histiocytosis (67, 68). Third, importantly and unexpectedly, LCH-1 showed that poor response to initial 6-week therapy in children with risk-organ involvement was an adverse prognostic factor. Stratification of children into low-risk and high-risk groups was based on findings from LCH-II. The aim of clinical trial LCH-III, which opened for patient accrual in 2001, is to evaluate the relative efficacies of two multiagent treatment regimens (prednisone, vinblastine, and 6-mercaptopurine (6-MP), with or without methotrexate) in patients with multisystem Langerhans cell histiocytosis considered to be at high risk of disease progression or recurrence (19). This clinical trial will examine whether methotrexate improves the outcome of patients with high-risk Langerhans cell histiocytosis and will define optimal treatment for patients with lower-risk disease, such as multifocal bone disease.

A new international cooperative study of adult Langerhans cell histiocytosis opened in 2004 (LCH-A1) and continues to accrue patients (41). The aims of LCH-A1 include the following: (1) defining a uniform initial evaluation for adults

with single-system disease, central nervous system lesions, isolated pulmonary disease, and multisystem Langerhans cell histiocytosis; (2) evaluating the effectiveness of a standard multiagent chemotherapy protocol in adults with multisystem Langerhans cell histiocytosis; and (3) evaluating the effectiveness of smoking cessation and of steroid therapy in adults with isolated pulmonary Langerhans cell histiocytosis. Adults with single system disease who are enrolled in the LCH-A1 clinical trial will receive 6 weeks of prednisone and vinblastine followed by continuation treatment with 6-mercaptopurine, prednisone, and vinblastine for 6 months. Under the LCH-A1 clinical trial, adults with multisystem disease will also receive prednisone and vinblastine for 6 weeks, followed by continuation treatment with 6-MP, prednisone, and vinblastine for 6 or 12 months. Patients with solitary pulmonary disease who stop smoking have a high rate of regression; thus, smoking cessation is essential for patients with lung disease. Those who have persistent lung disease after a trial of smoking cessation (typically 6 weeks) might benefit from a course of steroids. Chemotherapy will be reserved as salvage therapy for patients with progressive lung disease despite not smoking and receiving treatment with steroids.

Radiation therapy has traditionally been reserved for residual disease, disease that recurs following curettage, lesions that increase in size, or lesions in a critical site, such as the orbit, mandible, or vertebral column, and might be needed for lesions that are unusually large and painful or occur in inaccessible areas (69). Radiation therapy is mandatory in patients who develop diabetes insipidus. PUVA has also been used for extensive skin disease or for cutaneous disease in a multisystemic form of Langerhans cell histiocytosis.

Salvage therapy with 2-chloro-2'-deoxyadenosine (2CdA) for patients with recurrent or progressive Langerhans cell histiocytosis following standard therapy is the focus of protocol LCH-S-98, which was recently closed to patient accrual (19, 70). The results are not yet published, but preliminary data evaluation showed that monotherapy with 2CdA does not significantly improve prognosis in patients with severe progressive Langerhans cell histiocytosis. However, 2CdA has shown promise in combination chemotherapy and remains to be studied further.

About 20% of the patients with multisystem Langerhans cell histiocytosis do not respond to the currently available first-line treatment and have extremely poor prognosis. A phase II prospective trial salvage protocol (LCH-S-2005) for patients with severe disease (involvement of liver, spleen, or hematopoietic system) who do not respond to at least 6 weeks of "conventional" therapy will soon be opened for patient accrual (19). This study is expected to assess the efficacy of a potentially more toxic combination therapy (2CdA and cytosine arabinoside) in Langerhans cell histiocytosis patients with extremely poor prognosis.

Patients with resistant multisystem disease have been reported to undergo allogeneic hematopoietic cell transplantation or chemotherapy followed by transplantation of affected organ (kidney, lung, or liver), but the true efficacy of these transplants is not yet known, as no widely disseminated clinical trials have been conducted (71–73). Other emerging therapies include the use of immunomodulatory agents such as thalidomide or monoclonal antibodies directed against the CD1a or CD52 epitopes found on Langerhans cells (74,75). Specific therapies

directed against the cytokines that are apparently critical to the abnormal proliferation have not yet been defined. Cooperative trials examining the efficacy and optimal treatment plan for these therapeutic options would be important to develop.

17.8 Clinical Course

The clinical course of the disease is greatly influenced by the number of affected organs at presentation, especially if involvement is accompanied by organ dysfunction (2, 4, 8, 10). Also, as previously stated, response to therapy at 6 weeks is an important prognostic variable (41–43). Age and histologic features such as nuclear atypia and mitotic rate are not independent prognostic indicators (41–43).

In one large study, those children who responded at 6 weeks to multiagent chemotherapy had a 3-year survival of 94%; that dropped to 34% in children who did not have a favorable 6-week response to chemotherapy (42). A recent study of adults with Langerhans cell histiocytosis showed that patients with "single-system disease" have a 5-year event-free survival of 100%, patients with solitary lung involvement have a 5-year event-free survival of 87.8%, and patients with multisystem disease have a 5-year event-free survival of 91.7% (10). The annual death rate in adults is estimated at 1.1% and a 5-year survival rate of >90% has been calculated (10). Disease recurrence in children varies, but it is approximately 50% in multifocal bony disease treated with single-agent chemotherapy, radiotherapy, or observation (43, 66).

Approximately 70% of patients with multisystem involvement develop late effects of Langerhans cell histiocytosis compared to approximately 24% of single system patients (43, 76). Diabetes insipidus, orthopedic abnormalities, and hearing loss are the most common problems. Neurologic problems, particularly cerebellar symptoms, might not manifest until 10 years or more after initial diagnosis. Endocrine abnormalities other than diabetes insipidis, such as growth hormone deficiency, may appear later in the course, possibly secondary to disease infiltration and secondary physical pressure by a growing tumor. Impaired liver function and therapy-related second neoplasms are other long-term adverse sequelae (33).

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