### Langerhans Cell Histiocytosis

**Synonyms:** Histiocytosis X, Langerhans cell granulomatosis, eosinophilic granuloma, Hand-Schüller-Christian disease, Letterer-Siwe disease, self-healing reticulohistiocytosis, Hashimoto-Pritzker syndrome

**Etiology:** Unknown, a clonal or reactive expansion of Langerhans cells infiltrating various organs

**Associations:** May coexist, precede, or follow the development of various solid tumors and hematopoietic malignancies

**Clinical:** Polymorphous: red-brown purpuric scaly papules, lichenoid papules, purpura, vesicles, pustules, erosions, ulcers of head, neck, trunk, mucosa, sometimes prominently involving intertriginous areas; may be solitary or extensive

**Histology:** Superficial dermal mononuclear cells with abundant eosinophilic cytoplasm, lobulated and clefted nucleus often with “coffee-bean” or reniform appearance; epidermotropism common

**IHC:** CD 1a+, S100+, CD68+

**Ultrastructure:** Deep nuclear cleaving, Birbeck granules (cytoplasmic linear tubular structures with inner serrations and terminal bulbous dilations, “tennis racquet-like”)

**Evaluation:** Radionuclide studies, chest radiograph, radiographs of areas of bone pain, urine specific gravity

**Treatment:** Excision of solitary lesions, curettage of solitary bone lesions, with or without low-dose irradiation; for multifocal disease, observation or prednisone, vinblastine, or methotrexate

**Prognosis:** Excellent for unifocal disease if no progression to multifocal disease within two years; multifocal disease is associated with limited mortality, primarily due to respiratory failure or cor pulmonale

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Langerhans cell histiocytosis (LCH) refers to a collection of syndromes, characterized by infiltration of various tissues by Langerhans cells. In 1941, Farber suggested that eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller-Christian disease all represent different manifestations of a single pathologic process, and in 1953, Lichtenstein used the term “histiocytosis X” to encompass these entities (1,2). Subsequent to the description of Birbeck granules as a specific ultrastructural marker for Langerhans cells (3), the infiltrating cells of histiocytosis X were identified as Langerhans cells. In 1987, the Writing Group of the Histiocyte Society proposed that *Langerhans cell histiocytosis* replace the term *histiocytosis X* as more appropriate (4).

Paul Langerhans first observed the cell that bears his name in the epidermis in 1868. The function of the Langerhans cell remained a mystery until recently. Langerhans cells are dendritic antigen-presenting cells that normally reside within squamous epithelium, periepithelial connective tissue, lymphatics, and in areas of lymph node.
They are important in antigen processing that occurs in the development of contact dermatitis.

Studies to date suggest that LCH is a heterogeneous disease with an unclear etiology. A clonal expansion of Langerhans cells has been demonstrated in many cases (5,6). However, an analysis of pulmonary LCH found that the majority of nodules were not clonal, suggesting that some forms of the disorder may be reactive (7). Cigarette smoking was suggested as a possible stimulus in reactive cases. Also supporting a reactive nature in some cases of LCH is the observation of a close pathological association of lesions of LCH with associated malignancies, particularly lymphomas and lung carcinomas (8). Nodular collections of LC have also been observed in close association with lymph node metastatic melanoma (9).

A possible infectious etiology of LCH has been explored. One investigation identified human herpesvirus-6 in lesional tissue (10), but another did not find any evidence of genomes for adenovirus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, human herpesvirus-6, human immunodeficiency virus, human T-cell leukemia viruses, or parvovirus (11). A familial clustering has been reported, supporting a genetic factor in the development of the disease (12). Chromosomal translocations and an increase in chromosome breaks have been reported in LCH lesions, possibly due to genetic chromosomal instability, viral infection, or chromosomal injury from toxic environmental exposures (13). There is some epidemiologic evidence linking LCH to cigarette smoking, solvent exposure, family history of benign tumors, blood transfusions, and urinary tract infections during pregnancy. Cigarette smoking, in particular, has been linked to pulmonary LCH (14). LCH has also been reported in association with malignant neoplasms (8,15,16). Approximately two-thirds occur in association with lymphomas or leukemia, and one-third, with solid tumors, most commonly lung carcinoma (8). Most cases of malignancy-associated LCH occur after the malignant diagnosis, suggesting a possible therapy-related etiology.

Cutaneous lesions of LCH have a wide range of morphologies. These include papules or plaques that may be scaly or eroded, bullae, vesicles, ulcers, petechiae or purpura (Figures 4.1 and 4.2). The lesions may be solitary, but in widespread disease tends to favor scalp and intertriginous areas, following an anatomic distribution similar to that of seborrheic dermatitis, which it may resemble. Solitary or multiple lesions of the external genitalia may also occur. Because patterns of cutaneous LCH do not appear to be predictive of underlying disease, diagnostic studies should be undertaken in all cases, even if there is limited cutaneous involvement (see evaluation listing below).

Biopsy specimens of LCH contain an infiltrate of Langerhans cells (LC), usually within the papillary and superficial reticular dermis, sometimes in greater density around adnexal structures (17), often demonstrating varying degrees of epitheliotropism (Figure 4.3A and 4.3B). The individual cells are 10–12 µm, with eosinophilic cytoplasm and convoluted, sometimes reniform nuclei. Small nucleoli may be apparent. Mitotic figures are uncommon. By contrast, foci of necrosis are common, and

![Figure 4.1. Coalescing red-brown papules with flexural accentuation.](image-url)
4. Langerhans Cell Histiocytosis

correlate with the frequent clinical scenario of erosion and sometimes ulceration. LC are frequently admixed with eosinophils. Multinucleated cells and lipidized macrophages are seen in some lesions, but there is no evidence that these are LC (15,18). Given overlapping morphology with other cells, additional confirmatory studies should be undertaken. These include immunohistochemical staining with antibodies to CD1a, displaying a membranous pattern (18). LC are also labeled by antibodies to S100 and peanut agglutinin, but not by histiocytic markers such as muramidase or HAM56 (15). Prior to the development of antibodies to CD1a, a specific diagnosis of LC required ultrastructural identification of Birbeck granules. Birbeck granules are linear cytoplasmic granules with interior serrations and occasional bulbous “tennis racquet-like” terminal dilations that are thought to arise from cell membrane and may show membrane connections. Their formation is known to be induced by a C-type lectin cell surface receptor, langerin. Langerin (CD207) is a more specific marker of LC than is CD1a and may eventually supplant its use as a diagnostic tool (19). The role of langerin and Birbeck granules is unknown, but they do not appear to be necessary for principal LC functions (20).

Mucocutaneous involvement in LCH should be taken in the context of involvement of other organ systems. Combining the two largest single center series, 67% of LCH cases involve a single organ system, bone being by far the most frequent (15,16). When looking at both single-system and multisystem disease, bone involvement occurs in 70%, followed by pulmonary in 18%, and mucocutaneous involvement in 16%. Of those with mucocutaneous involvement, approximately one fifth have disease limited to the skin (15). Evaluation of data from the French Langerhans’ Cell Histiocytosis Study Group, a pediatric population, and the adult cases from the International Registry of the Histiocyte Society, suggests a greater incidence of pulmonary disease in adults (58%, versus 9% in the pediatric population) (21,22).

Having made a diagnosis of cutaneous Langerhans cell histiocytosis, it is important to perform an additional diagnostic evaluation for multisystem disease, since most cutaneous presentations are accompanied by other organ system involvement. Appropriate evaluation is directed by clinical symptoms and signs. General guidelines are suggested:

**Figure 4.2.** Red-violaceous scaly papules with hemorrhagic crust.

**Figure 4.3.** (A and B) Ulcerated papule with wedge-shaped and epitheliotropic infiltrate of Langerhans cells with amphophilic cytoplasm and eccentric reniform nuclei.
Evaluation of the Patient Presenting with Cutaneous Langerhans Cell Histiocytosis

1. Thorough physical examination with attention to lymph nodes, liver, spleen
2. Bone scan with radiographs of symptomatic areas
3. Chest radiograph
4. Random urine specific gravity and serum uric acid as screen for diabetes insipidus; vasopressin challenge test to confirm if screen suggests
5. Complete blood count with differential, platelets
6. Liver enzyme tests if hepatomegaly is present

Should no evidence of multifocal disease be present, close clinical follow-up in the first two years is advised since additional foci of disease are most likely to become apparent in that time period (15).

Prognosis in LCH is generally favorable. Large series have shown low mortality directly due to disease, the most frequent cause being respiratory failure associated with pulmonary disease (15,16). There may be considerable morbidity and mortality associated with treatment (15). Deaths due to overwhelming LCH are exceptional. Long-term complications from the disease include pituitary dysfunction or diabetes insipidus, each occurring in approximately 25% of patients, and a neurodegenerative syndrome occurring in approximately 10% of patients with long-term follow-up (23).

Treatment for LCH is determined by extent and type of organ system involvement. Isolated bone lesions are best treated with curettage. If the lesions are in critical weight-bearing bones, low-dose irradiation may be added. Systemic treatment most commonly consists of prednisone, followed by vinblastine, or methotrexate. It has been emphasized that doses associated with bone marrow depression or other toxicities are not generally required for a good therapeutic response (15). 2-deoxychloro-adenosine administration has also produced favorable outcomes (24). Hematopoietic stem cell transplantation has been used in some cases of severe refractory LCH with complete remission, but death may occur from therapy (25).

Cutaneous LCH has been treated effectively with topical nitrogen mustard (26). Additional therapeutic modalities for cutaneous and mucosal disease have included topical steroids (15), PUVA (27), thalidomide (28), and α-interferon (29). Should disease resolution occur, clinical follow-up is advised because of potential for long-term complications, recurrence of disease, or the development of associated malignancy.

References


