Langerhans Cell Histiocytosis Presenting in the Neonatal Period

A Retrospective Case Series

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Objectives: To describe the morphologic characteristics of skin lesions, extent of extracutaneous disease, and outcomes in patients with neonatal presentation of Langerhans cell histiocytosis (LCH), and to examine clinical predictors of disease prognosis.

Design: Retrospective validation cohort study. Maximum duration of follow-up was 10 years.

Setting: A tertiary care children’s hospital in Chicago, Ill.

Patients: Nineteen children with cutaneous findings in the first 4 weeks of life and subsequently diagnosed with LCH based on compatible tissue histologic analysis, confirmed by electron microscopy and/or immunohistochemical analysis.

Main Outcome Measure: Cutaneous lesion morphologic characteristics, extracutaneous manifestations, treatments, and outcomes were tabulated and compared.

Results: The most common initial skin lesion was erythematous, often crusted, vesiculopustules. Skin lesion morphologic traits did not correlate with extent of extracutaneous disease. One third of patients had disease limited to the skin and/or mucous membranes. All of these patients are alive and well, and 1 has developed diabetes insipidus. Twelve of the 19 patients had multisystem disease, and 2 died of disease. The results of a multorgan workup performed at the time of diagnosis were predictive of which patients in this cohort manifested multisystem disease. The overall incidence of diabetes insipidus was 21%.

Conclusions: Vesiculopustular lesions are common in congenital/neonatal LCH, but the morphologic characteristics of lesions are not helpful in predicting the extent of disease. A multorgan evaluation at the time of diagnosis may be predictive of the probability of multisystem involvement with LCH.


THE HISTIOCYTOSES are a group of disorders that encompasses a wide range of primary and secondary, solitary and multiple, and benign and malignant conditions. They are unified by their common cell of origin, the histiocyte. The clinical findings associated with these conditions depend on the extent of organ systems involved. Several classification schemes have been proposed to better delineate the specific conditions and to decrease confusion stemming from the historical use of multiple eponyms. The most familiar classification includes Langerhans cell histiocytosis (LCH), non-Langerhans cell histiocytoses, and malignant histiocytic disorders. The presence or absence of the pathognomonic Langerhans cell organelle, the Birbeck granule, within the pathologic histiocyte, and the findings on immunohistochemical studies help in distinguishing these various disorders.

Patients with LCH demonstrate a variety of clinical presentations and possible outcomes. The term LCH and the historical term histiocytosis X encompass 3 classic clinical entities, which are now considered to be variations of the same disease: (1) eosinophilic granuloma (localized lesions in bone); (2) Hand-Schuller-Christian disease (multiple organ involvement with the classic triad of skull defects, diabetes insipidus [DI], and exophthalamos); and (3) Letterer-Siwe disease (visceral lesions involving multiple organs). A fourth clinical entity termed congenital self-healing reticulohistiocytosis (Hashimoto Pritzker variant) has been described in which skin lesions are present at birth, accompanied in rare cases by systemic findings, and with complete spontaneous involution within 2 to 3 months. Particularly challenging are those patients presenting as newborns with a diverse array of less classic skin lesions such as...
Methods

Nineteen patients with LCH onset with cutaneous involvement within the first 4 weeks of life were seen at Children’s Memorial Hospital from 1988 to 1998. A retrospective review of the medical records from the pediatric dermatology clinical database at Children’s Memorial Hospital was performed, along with a review of relevant photographic documentation of the cutaneous lesions, if available. The following parameters were evaluated: age when signs and symptoms initially manifested, morphologic characteristics of cutaneous lesions, age at diagnosis, additional organ involvement, therapy administered, course, and outcome, including delayed sequelae. Diagnosis was contingent on tissue biopsy with routine histopathologic analysis revealing changes consistent with LCH and with confirmation by electron microscopic findings of Birbeck granules, and/or S100 or CD1a positivity on immunostaining.

Routine histopathologic analysis was performed on full-thickness biopsy specimens obtained by punch biopsy of involved skin. All specimens were fixed in formalin solution, embedded in paraffin, sectioned, and stained with hematoxylin-eosin for light microscopic examination. Histologic interpretation was performed by experienced pathologists and dermatopathologists in our institution.

Electron microscopy was performed on fresh tissue fixed in Karnovsky medium (paraformaldehyde-glutaraldehyde). Postfixation was performed in 2% osmium tetroxide in the same buffer. Tissue was dehydrated through graded concentrations of ethanol, 50% through absolute, and propylene oxide and embedded in Spurr and Araldite resin. Ultrathin sections were cut at 60 to 70 nm using an ultramicrotome and were stained with saturated uranyl acetate in water and then with Reynolds lead citrate. Stained sections were studied in an electron microscope at an accelerating voltage of 75 to 100 kV.

Immunostaining was performed on paraffin-embedded tissue sections labeled with S100 polyclonal antibody (Dako Corp, Carpenteria, Calif) or CD1a monoclonal antibody (Immunotech, Marseille, France). Sections were deparaffinized and stained with the avidin-biotin complex procedure (Vectorstain Elite ABC Kit with DAB chromogen; Vector Laboratories, Burlingame, Calif).

Results

Table 1 summarizes patient characteristics, presentation, treatment, and clinical course. Nineteen patients were followed up for a mean of 3.2 years (range, 2 months to 10 years). Thirteen (68%) of 19 patients were male. Fourteen of the 19 patients had skin lesions noted at birth. In all but patient 7, the diagnosis was ultimately made by skin biopsy. In this patient, the diagnosis was rendered based on results of lymph node biopsy; the skin lesions were clinically consistent with the seborrheic form of LCH. The mean age at diagnosis was 3.5 months (range, 2 days to 20 months). Delays in diagnosis were owing to misdiagnoses such as psoriasis and other chronic dermatitis prior to presentation to our institution.

Twelve (63%) of the 19 patients had multisystem disease, defined as involvement of skin and/or mucous membranes, as well as at least 1 other system, including bone, lymph nodes, mastoids or middle ears, central nervous system, eye, gastrointestinal tract, bone marrow, or solid organs. Diabetes insipidus was considered separately. The remaining 7 (37%) of 19 patients manifested purely cutaneous and/or mucous membrane ("limited") disease. One of these 7 patients (patient 17) developed DI at age 3 years.

The various morphologic traits of skin lesions are listed in Table 2. Most common were erythematous vesiculopustules (Figure 1), often with crusting (10 patients). Eczematous scaling lesions in a seborrheic-like distribution (Figure 2) were also common (7 patients) and tended to present later, within the first month of life. Oral mucosal lesions, including erosions (Figure 3) and petechiae, were seen in 4 of the patients (20%). There was no clear difference between the morphologic characteristics of the mucocutaneous lesions in those who had multisystem disease vs those with limited disease, although all of the patients with limited disease had skin lesions present at birth. Only one of the patients with limited disease had lesions with an eczematous/seborrheic dermatitis appearance.

The diagnosis of LCH was confirmed in 18 of 19 cases by histopathologic examination of skin biopsy samples; in 1 patient the diagnosis was based on the results of lymph node biopsy. There were no significant differences in histopathologic findings between patients with multisystem disease and those with limited disease. Representative skin sections routinely stained with hematoxylin-eosin revealed a primarily dermal infiltrate composed of aggregates of large histiocytic cells with eccentrically placed grooved nuclei, having the appearance of being folded. The cells had abundant eosinophilic cytoplasm and displayed epidermotropism. Findings from electron microscopic study revealed characteristic Birbeck granules in these histiocytes. Immunohistochemical stains for S100 and/or CD1a highlighted these same histiocytic cells.

In all of these patients, a comprehensive workup for systemic disease was performed at the time of the histopathologic diagnosis of LCH. This workup included a care-
ful physical examination with attention to examination of lymph nodes and abdominal organs, complete blood cell counts, blood chemistry profile with liver function tests, coagulation studies, urine osmolality, and skeletal and chest radiography. When indicated, additional imaging studies such as computed tomography scans and ultrasonograms were obtained. Bone marrow biopsies were performed for 6 patients. Evaluation of the bone marrow was performed at the discretion of the treating physician for staging purposes in 5 patients and in response to leukopenia and disease progression in the sixth patient. Multiorgan involvement was discovered at the time.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age at Presentation</th>
<th>Presenting Symptoms</th>
<th>Age at Diagnosis</th>
<th>Organs Involved</th>
<th>Treatment</th>
<th>Clinical Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>&lt;1 mo</td>
<td>Skin lesions</td>
<td>11 mo</td>
<td>Bone, ears/nose/throat</td>
<td>Prednisone, vinblastine</td>
<td>NAD at age 5 y, receiving main vinblastine</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>2 mo</td>
<td>Bone, liver, lungs, mucous membranes</td>
<td>Methylprednisolone, vinblastine, etoposide, 6-mercaptopurine</td>
<td>NAD at age 2 y, receiving main vinblastine</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>11 wk</td>
<td>Bone, lymph nodes, liver, lungs, spleen</td>
<td>Prednisone, vinblastine</td>
<td>NAD at age 1 y, receiving main vinblastine</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>&lt;1 mo</td>
<td>Skin lesions, bloody diarrhea</td>
<td>3 mo</td>
<td>Bone, gastrointestinal tract, liver</td>
<td>Prednisone, vinblastine, etoposide</td>
<td>NAD at age 4 y, not receiving therapy</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>3 mo</td>
<td>Bone, mucous membranes</td>
<td>Prednisone, vinblastine, etoposide, 6-mercaptopurine</td>
<td>NAD at age 2.5 y, receiving prednisone, vinblastine, 6-mercaptopurine</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>6 mo</td>
<td>Eye, mucous membranes, central nervous system, pituitary</td>
<td>DDAPV, prednisone, methylprednisolone, etoposide</td>
<td>Blind, ataxic, and learning disabled; receiving DDAPV at age 8 y</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>&lt;1 mo</td>
<td>Skin lesions, otitis media</td>
<td>4 mo</td>
<td>Lymph nodes, ears/nose/throat</td>
<td>Surgical excision of affected lymph nodes</td>
<td>NAD at age 3 y</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>4 mo</td>
<td>Lungs, ears/nose/throat, mucous membranes</td>
<td>Dexamethasone, vinblastine</td>
<td>NAD at age 5 y</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>1 wk</td>
<td>Bone marrow, liver, spleen</td>
<td>Methylprednisolone, vinblastine</td>
<td>Deceased at age 4 mo with bacteremia and disseminated disease</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>&lt;1 mo</td>
<td>Skin lesions</td>
<td>20 mo</td>
<td>Lymph nodes, bone, pituitary</td>
<td>DDAPV, prednisone</td>
<td>Delayed verbal development, receiving prednisone, vinblastine, and DDAPV at age 3 y</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>&lt;1 mo</td>
<td>Skin lesions</td>
<td>14 mo</td>
<td>Bone, bone marrow, pituitary, eye, liver, ears/nose/throat, spleen</td>
<td>Prednisone, vinblastine, etoposide, methylprednisolone, methotrexate, cytoxan, cyclosporin, radiation therapy, vincristine</td>
<td>Deceased at age 3 y with cardiovascular collapse</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>2 d</td>
<td>Lymph nodes, lungs</td>
<td>Methylprednisolone, vinblastine</td>
<td>NAD at age 5 y</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>1 mo</td>
<td>None</td>
<td>None</td>
<td>NAD at age 3 y with scars</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>17 d</td>
<td>None</td>
<td>None</td>
<td>Lost to follow-up after 2 mo with scarring</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>1 wk</td>
<td>None</td>
<td>None</td>
<td>NAD at age 2 y with scars</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>3 d</td>
<td>None</td>
<td>None</td>
<td>NAD at age 8 mo</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>4 mo</td>
<td>Pituitary</td>
<td>DDAPV</td>
<td>Receiving DDAPV at age 10 y</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>1 mo</td>
<td>Mucous membranes</td>
<td>None</td>
<td>NAD at age 18 mo</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>Birth</td>
<td>Skin lesions</td>
<td>7 d</td>
<td>None</td>
<td>None</td>
<td>NAD at age 22 mo</td>
</tr>
</tbody>
</table>

*NAD indicates no active disease; DDAPV, 1-desamino-8-D-arginine vasopressin.

Table 2. Characteristics of 19 Patients With Congenital/Neonatal Langerhans Cell Histiocytosis

<table>
<thead>
<tr>
<th>Cutaneous Lesions</th>
<th>Sites Affected</th>
<th>Patient No. (Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vesiculopustules (crusting)</td>
<td>Scalp, face, palms, soles, trunk, generalized</td>
<td>2, 5, 6, 8, 9, 12, 13, 16, 18, 19 (18)</td>
</tr>
<tr>
<td>Eczematous (seborrhea-like) dermatitis</td>
<td>Groin, scalp, face, intertriginous, generalized</td>
<td>1, 4, 7, 9, 10, 11, 13 (7)</td>
</tr>
<tr>
<td>Mucosal lesions (erosions, petechiae, granulomas)</td>
<td>Buccal mucosa, gingiva</td>
<td>5, 6, 8, 18 (4)</td>
</tr>
<tr>
<td>Erythematous papules</td>
<td>Scalp, feet, groin, trunk</td>
<td>3, 8, 17 (3)</td>
</tr>
<tr>
<td>Nodular, ulcerative lesions</td>
<td>Dorsal foot, neck</td>
<td>14, 15 (2)</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Generalized</td>
<td>9 (1)</td>
</tr>
</tbody>
</table>
of the initial evaluations in all patients with multisystem disease: no patient with histologically confirmed cutaneous LCH and initial negative findings for systemic disease developed extracutaneous organ involvement during the subsequent period of observation, except for the delayed diagnosis of DI, which was diagnosed at age 2 to 3 years in all 4 patients with this disorder.

The mortality rate in our patients with multisystem disease was 16% (2/12), with death occurring at age 4 months owing to sepsis (patient 9) and at age 3 years owing to cardiovascular collapse (patient 11). These 2 patients were the only patients in the cohort with known bone marrow involvement. Of the surviving patients with multisystem disease, half (5/10) are in remission, currently receiving no therapy, and the other half (5/10) continue to receive maintenance chemotherapy. Most of these patients experienced resolution of their cutaneous and mucosal lesions within months of initiation of systemic therapy (range, 6-15 months). Those patients who developed DI continue to receive treatment for that condition. The therapies employed for each patient are given in Table 1.

All patients with limited disease are healthy and receiving no therapy, except for treatment of DI. None of these patients received systemic treatment, and all experienced resolution of the cutaneous and mucosal lesions. Topical treatment with corticosteroids and keratolytics was used intermittently in a number of cases without notable effect. Residual scarring was reported in 3 patients, 2 of whom presented with nodular lesions at birth, and 1 with vesiculopustules.

**COMMENT**

Our large series of neonates with LCH demonstrates the variety of cutaneous lesions and the inability to predict the extent of systemic involvement based on morphologic characteristics of the skin findings. Patients in this series who had disease limited to the skin and mucous membranes had an excellent outcome. The results suggest that the evaluation performed at the time of diagnosis is a good indicator of which patients will be affected by multisystem disease. Late development of DI occurred in 21% of our patients.

Typical cutaneous lesions of LCH are scaly, erythematous, seborrhea-like eruptions of brown to red papules, especially pronounced in the intertriginous zones. Superficial ulcerations within these dermatitic lesions are also described, resulting in weeping lesions suggestive of eczema. In fact, as we and others have shown, neonates commonly show vesiculopustular lesions that are easily mistaken for an infectious process, and the more classic "seborrheic" and "eczematous" lesions may be observed later in the course. In addition, congenital skin lesions have been described as papules, macules or nodules, some with central crateriform ulceration, with a red, brown, blue, or yellow color. These patients with nodular lesions, whether congenital or later, have generally had a better prognosis. Such lesions were observed infrequently in our series (2 patients), although each of these patients had limited disease. The variability in presentation of congenital/neonatal LCH contributes to the frequent delay in diagnosis, as observed in our series and those of other authors.

Presentation during the neonatal period and with clearing during the first 2 to 3 months has been termed congenital self-healing reticulohistiocytosis to emphasize the limited involvement and good prognosis in this subset of patients. We prefer avoiding the use of this confusing designation as the course of this disease cannot be predicted without a thorough evaluation and follow-up for extracutaneous organ involvement, although our findings suggest that a comprehensive
The presentation and prognosis of Langerhans cell histiocytosis are known to be quite variable. The congenital/neonatal presentation and subsequent progression of this disease have not been well described.

This retrospective review demonstrates that vesiculopustular skin lesions are common in neonatal disease, but lesion morphologic characteristics are not helpful in predicting the extent or course of disease. The probability of multisystem disease may be predicted by the findings of a multiorgan evaluation at the time of diagnosis. The mortality rate in this series was 16%, and the incidence of diabetes insipidus was 21%. The findings of this study add support to the existing literature emphasizing the need for comprehensive evaluation of patients and regular follow-up assessments.

Evaluation at the time of diagnosis may be prognostically helpful. In general, LCH seems to exist on a spectrum from benign to severe and localized to disseminated, with all forms demonstrating the same findings on histopathologic and immunohistochemical studies.

Much of the literature addressing outcomes in patients with LCH has not been specifically stratified for patients presenting with disease in the neonatal period. One of the first detailed studies of disease outcomes assessed the courses of 127 patients based on age and organ involvement. In this cohort, patients younger than 2 years at the time of diagnosis with multisystem involvement were found to have significantly greater mortality than the older age groups. The French LCH Study Group conducted a multicenter retrospective study of 348 cases of LCH to assess clinical manifestations, treatment response, and long-term prognosis. Patients were followed for a median of 35.5 months. The median age at diagnosis was 30.2 months, with 27% of patients diagnosed prior to age 1 year. Patients presenting in the neonatal period were not specifically identified. Cutaneous involvement was documented in 39% of patients; however, specific skin lesions were not described. The overall survival rate was 90% at age 4 years. Among those who died, the median age at diagnosis was 8.5 months. Five of these 9 patients had disease limited to the skin, although one of these patients went on to develop DI much later. Hashimoto et al summarized 15 previously published cases of what they define as “congenital self-healing reticulohistiocytosis,” although the skin lesions developed after birth in 2 of the patients. Two of the 15 patients had multisystem disease, and all patients had an excellent outcome, with follow-up periods of 8 months to 14 years. Longaker et al reported 4 cases also labeled congenital self-healing reticulohistiocytosis, and highlight the presentation of crusted papules at birth, as well as involvement of mucous membranes and gingiva. In this small series, one of the patients demonstrated relapse of cutaneous disease after apparent resolution of clinical disease, and one patient had multisystem disease at presentation which resolved, but a bony relapse developed at age 6 months. These cases again emphasize the imprecision of the “self-healing” label and highlight the importance of abandoning this nomenclature.

In 1989, the Histiocyte Society published guidelines for the management of patients with LCH. They suggested that the following minimum baseline studies should be performed: complete blood cell counts, including platelets; liver function tests; coagulation studies; chest radiography; skeletal surveys; and urine osmolality testing. It is suggested that these examinations be repeated at 6-month intervals if findings are normal. If abnormal, then further testing and/or appropriate follow-up is necessary. Bone scans, though less sensitive indicators of bony involvement, may provide complementary information.

The findings from these systemic evaluations are fundamental to directing future therapy in patients with LCH. Treatment recommendations should be tailored to the sites of involvement. Our experience shows that therapy is often unnecessary for patients with LCH localized to the skin. Although responses to topical steroid agents have been described, we have not found the use of topical steroids to alter the disease; furthermore, their use is associated with the risk of local adverse effects and systemic absorption. Topical mustard and topical psoralen with UV light (PUVA) treatment have been advocated for cutaneous lesions, but use of these agents may predispose patients to the later development of malignancy. Severe cutaneous disease has been treated with the same systemic agents used to treat multisystem disease. In our experience, the response of the cutaneous lesions to these systemic agents is rapid. Treatment of single bony lesions is often localized to the affected site, including curettage or intralesional instillation of steroids. Other treatments for bony lesions include low-dose radiation (4000-8000 rad [40-80 Gy]) and non-steroidal anti-inflammatory drugs. The approaches to...
multisystem disease are varied and complex, with commonly used agents including prednisolone, vinblastine, and etoposide.

Our findings demonstrate that congenital/neonatal LCH may present with a variety of cutaneous morphologic characteristics, and a high index of suspicion must therefore be maintained. The most common morphologic trait of skin lesions in these patients appears to be erythematous vesiculopustules. Skin biopsy with immunohistochemical and ultramicroscopic evaluation is helpful in confirming the diagnosis. The extent of disseminated involvement cannot necessarily be predicted based on clinical or microscopic characteristics of the skin lesions, and a thorough multiorgan evaluation is indicated at the time of diagnosis and is useful in guiding therapy. Neonates with disease limited to skin and/or mucous membranes at the time of initial evaluation do not necessarily require therapy, may be less likely to develop multisystem disease, and seem to have a good prognosis. Importantly, though, patients who appear to have mild or self-limited LCH should continue to undergo periodic routine surveillance, as spontaneous resolution of skin lesions does not rule out the possibility of eventual progression or relapse, either in the skin or at extra-cutaneous sites. Our study is limited by suboptimal follow-up data for several patients and by weaknesses inherent to any retrospective review, and thus the significance of our findings in patients with congenital/neonatal LCH requires further elucidation. Continued study and outcomes analyses of this patient population are warranted.

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