An Infant With Recurrent Maculopapular Rashes, Anemia, Lymphadenopathy, and Hepatosplenomegaly

Jianxiong R. Bao, MD, PhD; Amal Anga, MD; Xin Gu, MD; Songlin Zhang, MD, PhD; and James D. Cotelingam, MD

Figure 1. A) Abdominal skin rash. B) Histologic section of the skin biopsy of Langerhans cell histiocytosis (hematoxylin and eosin, original magnification X400). C) Immunohistochemical staining for S-100 (original magnification X400). D) Immunohistochemical staining for CD1a (original magnification X400).
CASE REPORT

An 8-month-old black boy was admitted with a history of recurrent hemorrhagic maculopapular rashes especially concentrated over the abdomen (Figure 1A), and also on the chest, shoulder, hands, and groin. The rashes first appeared when he was six weeks old. Rashes initially were white, dome shaped but rapidly became erythematous, crusted and maculopapular. The child was toxic, febrile, anemic, and thrombocytopenic. The significant findings of physical examination included abdominal distention, cervical and inguinal lymphadenopathy, hepatosplenomegaly, and pedal edema. He was born as the third child of a nonconsanguineous marriage and was fully immunized. Developmental milestones were normal. There was history of dyspnea at birth. A family history is significant for eczema (brother), psoriasis (mother), and asthma (two brothers). There was no family history of malignancy.

Laboratory investigation at admission showed 7.2 g/dL total hemoglobin concentration, hematocrit packed cell volume 21.1%, C-reactive protein 5.85 mg/dL, erythrocyte sedimentation rate 12 mm/hr, white blood cell count 12,000/µL, platelets 62,000/µL, lactate dehydrogenase 306 U/L (High), total protein 4.2 g/dL (low), albumin 2.2 g/dL (low), calcium 8.5 mg/dL (low), IgA 55 mg/dL, IgG 387 mg/dL, and IgM 32 mg/dL (low for age). The urine analysis was normal. Blood cultures, human immunodeficiency virus, venereal disease research laboratory, Epstein-Barr virus, Parvovirus panel, and Glucose-6-phosphate dehydrogenase deficiency tests were all negative. Abdominal ultrasound, skeletal survey, X-rays of chest (posterior to anterior view), chest, shoulder, hands, and groin. The rashes first appeared when he was six weeks old. Rashes initially were white, dome shaped but rapidly became erythematous, crusted and maculopapular. The child was toxic, febrile, anemic, and thrombocytopenic. The significant findings of physical examination included abdominal distention, cervical and inguinal lymphadenopathy, hepatosplenomegaly, and pedal edema. He was born as the third child of a nonconsanguineous marriage and was fully immunized. Developmental milestones were normal. There was history of dyspnea at birth. A family history is significant for eczema (brother), psoriasis (mother), and asthma (two brothers). There was no family history of malignancy.

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CLINICAL PATHOLOGIC CORRELATION

Skin biopsy showed dense lichenoid cellular infiltration in the papillary dermis. Clusters and sheets of large ovoid cells had abundant eosinophilic cytoplasm and indented nuclei, and some nuclei appear “coffee-bean” shape. Some cells invaded into the epidermis, and admixed other inflammatory cells include lymphocytes and eosinophils (Figure 1B). Immunohistochemical staining of these cells were positive for S-100 (Figure 1C) and CD1a (Figure 1D), indicating the Langerhans cell nature of them. The diagnosis of Langerhans cell histiocytosis was rendered. Bone marrow biopsy showed some infiltration by similar cells and they were also positive for CD1 and S100, which is consistent with focal bone marrow involvement by Langerhans cells histiocytosis. Subsequently, the cervical lymph node biopsy also showed involvement of the disease.

Following the tissue diagnosis, the child was started on antipyretics, systemic antibiotics, topical agents, and chemotherapy. With exception of his abdomen most of his rashes resolved after he was started on chemotherapy.

DISCUSSION

Langerhans cell histiocytosis (LCH) is a rare disorder with an incidence of eight to nine cases per million per year in children and as many cases in adults as in childhood.1 The clinical presentation of LCH is heterogenous, ranging from a single system involvement, generally benign, to a multisystem life threatening disease. In the past, LCH was subdivided into three categories: Letterer-Siwe disease (acute disseminated disease), Hand-Schuller Christian disease (multifocal or uni-focal disease), and Eosinophilic granuloma (usually uni-focal disease) (Table). These three conditions are now considered different expressions of the same basic disorder. In 1990, the LCH Study Group adopted a stratification system with division of LCH into two major categories: single system LCH and multisystem LCH.2 Single system LCH is subdivided further into single site and multiple sites. Multisystem LCH is defined as involvement of two or more organs at diagnosis with or without organ dysfunction. The criteria for the diagnosis of LCH defined by the Histioocyte Society Writing group is classical LCH histopathology confirmed by the presence of Birbeck granules on electron microscopy or by demonstration of CD1a on immunohistochemistry.3 Under the electron microscope, Birbeck granules have a pentalaminar, rodlike, tubular appearance and sometimes a dilated terminal end (tennis racket appearance). The presence of Birbeck granules can be more easily proven now by immunohistochemical staining of Langerin (CD207). An unusual form of histiocytosis, namely congenital self-healing reticulohistiocytosis (CSHRH or Hashimoto-Pritzker disease) generally follows a benign clinical course and its incidence may be underestimated due to a high rate of spontaneous resolution and lack of clinical recognition.4 The pathogenesis and etiology of LCH, whether it is a reactive rather than a neoplastic disorder, remain unanswered.5 The detection of clonal histiocytes in all forms of LCH has been used as evidence that this disease is a clonal neoplastic disorder.6 Familial clustering of LCH has been documented, and twin studies have shown a higher rate of concordance for LCH in monozygotic (92%) twin studies have shown a higher rate of concordance for LCH in monozygotic (92%) twin studies have shown a higher rate of concordance for LCH in monozygotic (92%) twin studies have shown a higher rate of concordance for LCH in monozygotic (92%)

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<td><strong>Subtypes</strong></td>
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versus dizygotic (10%) twins. These findings indicate the possibility of a germ line mutation in some patients that may predispose them to LCH. The alternative hypothesis is that LCH is a reactive disease in the setting of immature dysregulation leading to an aberrant reaction between Langerhans cells and T lymphocytes. More recently, novel gene and pathways may contribute to LCH have been identified. Osteopontin, vanin-1 and neuropilin-1, whose products activate and recruit T-cells to sites of inflammation, were highly expressed in LCH cells. In keeping with this reactive hypothesis, a recent study failed to show gross genomic abnormalities by a multi targeted molecular approach, which suggests that LCH may be the result of restricted oligoclonal stimulation rather than an unlimited neoplastic proliferation.

The clinical presentation is variable. One-third of patient with LCH present with an isolated osseous lesion. A third present with non-osseous single system disease, and the remaining third present with multiple organ disease. The most common organ involved in non-osseous uni-system LCH is the lung. The clinical features of LCH are non-specific and generalized. The top five clinical manifestations, in decreasing order of frequency, are local bone pain, dyspnea, malaise with abnormal chest X-ray, painful scalp nodules, and spontaneous pneumothorax.

Skin rash, lymphadenopathy, endocrine, and bone marrow involvements are also seen. Pulmonary LCH is considered to be a benign condition in adults. But there is increasing recognition that it is a smoking related interstitial lung disease and, if untreated, long term complications may include pulmonary hypertension or respiratory failure.

Acute disseminated LCH (Letterer-Siwe disease) usually occurs in infants, but can be seen in older children. The most common manifestations are fever, anemia, thrombocytopenia, enlargement of the liver and spleen, lymphadenopathy, and pulmonary infiltrates. Cutaneous lesions are found in 80% of cases, and present as a seborrheic dermatitis like skin rash. Lesions crust and scale, may manifest as vesicopustular and purpuric eruptions in crops over the face, scalp, and trunk. Nail bed involvement is not uncommon. Infants with only cutaneous eruption have a good prognosis, but multisystem involvement including the lungs, liver and bone marrow, and spleen are associated with high mortality. Hepatosplenomegaly occurs sometimes with ascites. Splenomegaly is usually associated with bone marrow involvement. Splenic enlargement is due to infiltration by LCH or is secondary to portal hypertension with liver disease. Solitary bone lesions or single system involvement generally occurs in older children. Osteolytic lesions are uncommon except in the mastoid region of the
and medical institution. Presently he awaits stem cell transplantation at another medical institution. A poor response to primary as well as salvage chemotherapy.

The treatment of LCH depends on the extent and severity of the disease at diagnosis. Patients with single-system LCH generally have a high chance of spontaneous remission and a favorable outcome. The goal of treatment for these patients is to preserve normal activity and prevent long term sequelae. Disease reactivation can occur in up to 25% of patients with multifocal bone LCH, and in 50%-70% of those with bone LCH as part of multisystem disease. Several clinical trials have been done for multisystem LCH. In 1991, the first international randomized chemotherapy trial LCH-I for patients with multisystem LCH was initiated by the Histioyte Society. It compared six month single agent therapy with vinblastine or etoposide, and the study showed both drugs were equally effective in terms of survival and disease response. The second randomized controlled trial, LCH-II (1996-2000), was designed to evaluate the addition of etoposide to vinblastine and prednisone in multisystem risk organ positive (RO+) patients or patients less than two years of age. Patient less than two years of age, and RO+ had a 100% survival and a high (>80%) rate of rapid response. RO+ patients not responding within six or 12 weeks had a high mortality (75%). The most recent LCH-III trial (2001-2007) was designed to assess the value of the addition of methotrexate to the standard two drug protocol for RO+ patients and to evaluate whether prolonging therapy to 12 months would decrease the reactivation rate and rate of permanent consequences in RO- patients. The final analysis of the results is underway at present. More information can be reached on the Histiocyte Society website at www.hstio.org. Patients with multisystem LCH who fail to respond after two courses of therapy have a poor outcome. Treatment of these refractory patients and of those with multiple reactivation has proved to be challenging. The combination of Ara-c, vincristine, and prednisolone was shown to be effective in LCH patients with organ dysfunction and those with relapsed disease. However, none of combination chemotherapy appears to improve survival in patients with refractory disease. A number of successful stem cell transplants have been performed in high risk LCH patients with resistant RO involvement. Less than 50 cases transplanted for refractory LCH have been reported with good disease control, but with a high transplant related mortality. Our patient had multiple organ disease and had a poor response to primary as well as salvage chemotherapy. Presently he awaits stem cell transplantation at another medical institution.

Temporal bone, resulting in a clinical picture of otitis media. Patients with disseminated LCH seem to be at risk for a variety of systemic tumors, including lymphoma, leukemias, and lung tumors. Skin biopsy in Letterer-Siwe disease shows a proliferative reaction with extensive upper dermal infiltration and epidermal invasion with histiocytes, some of which are atypical, along with erythrocytes.

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REFERENCES


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