Langerhans cell histiocytosis with multisystem involvement in an infant: A case report

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Abstract. Langerhans cell histiocytosis (LCH) is a proliferative disease of histiocyte-like cells, with a wide range of clinical presentations that vary from a solitary lesion to more severe multifocal or disseminated lesions. The disease can affect any age group; however, the peak incidence rate is in infants aged between 1 and 3 years-old. Diagnosis of LCH should be based on the synthetical analysis of clinical presentations, in addition to features of imaging and histopathology. Although certain cases regress spontaneously, other patients require systemic chemotherapy together with the administration of steroids. The present study reports the case of an infant with LDH with multisystem involvement, including that of the bone, skin, orbit, spleen and lungs. The patient received chemotherapy and obtained rapid improvement in the involved systems. A total of 2.5 years after completion of the therapy, the patient still remains in follow-up and no evidence of active disease has been noted.

Introduction

Langerhans cell histiocytosis (LCH), previously known as histiocytosis X, is a proliferative disease of histiocyte-like cells. The condition is a rare disorder with several forms of clinical presentations, which include osteolysis, ulcerations of the skin and soft tissues, and occasionally viscera involvement (1). The majority of cases present as uni- or multifocal bone lesions, while visceral involvement is less common (2,3). The most frequent sites of a visceral manifestation are the lungs, followed by the skin and the lymph nodes (2-5). The etiology of LCH is yet to be completely understood, although certain forms of immunological dysfunctions have been implicated. LCH can occur at any age; however, the peak incidence is observed in individuals aged between 1 and 3 years (6). A

diagnosis of LCH should be based on the synthetic analysis of clinical presentations, as well as features of imaging and histopathology. Prognosis is dependent on a variety of factors, including the age of onset, the number of organs involved, the degree to which normal function of the organs is affected and the rate of disease progression (7,8). For the majority of children with LCH, the disease is self-resolving. However, for patients with multisystemic involvement, the most common treatment method is steroids and chemotherapeutic agents. The present study reports the case of an infant diagnosed with LCH with multisystem involvement, including that of the bone, skin, orbit, spleen and lungs.

Case report

Written informed consent was obtained from the patient's mother. An 11-month-old Chinese boy was admitted to the China-Japan Union Hospital of Jilin University (Changchun, China) following presentations of recurrent seborrheic dermatitis all over the skin, bilateral otorrhea and a mass on the scalp. The seborrheic dermatitis deteriorated, and ulcers developed on the skin of the bilateral groin. In addition, the patient had a high fever of up to 103˚F. A decreased willing to stand or cry was observed when the patient was standing, along with exophthalmos of both eyes, particularly in the left eye. Physical examination revealed a soft mass, measuring 1.5 cm in diameter, in the right parietal region. Furthermore, computed tomography (CT) scans demonstrated a round-shaped osteolytic lesion of the right parietal bone (Fig. 1) and erosion of the right scapula (Figs. 2-3). In addition, CT imaging revealed a soft tissue mass in the left posterior orbit (Figs. 4 and 5). Increased interstitial markings, with reticular patterns in the lungs (Fig. 6), and enlargement of spleen (Fig. 7) were also observed in the CT scans. A complete blood count from the patient revealed a hemoglobin level of 112 g/l, a white blood cell count of $6.1x10^9$/l and a platelet count of $456x10^9$/l. Anaplastic lymphoma kinase, liver and kidney function tests (alanine aminotransferase, 14 U/l; aspartate aminotransferase, 22 U/l; creatinine 1.0 mg/dl) were normal. A skin biopsy was performed and the results confirmed the diagnosis of LCH. Immunohistochemical staining produced the following results: CD1a, +++; fascin, +++; S-100, +++; Kp-1, sparsely +; phosphoglucomutase-1, -; Ki-67, >20%+.

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The patient subsequently received a chemotherapy regimen consisting of vindesine, etoposide and prednisone (VEP regimen). Following one cycle of chemotherapy, the patient's temperature returned to normal, with rapid improvement observed with regard to the dermatitis and otorrhea. In addition, the mass on the scalp decreased in size. The VEP regimen was then alternated with a VCP regimen, consisting of vindesine, cyclophosphamide and prednisone. After 12 cycles (one cycle every ~4 weeks), the patient was shifted to vinblastine therapy, which was applied every two weeks for one year, due to the major residual tumor burden. With completion of the therapy for ~2.5 years, the patient continues to undergo follow-up and no evidence of active disease has been observed.

Discussion

LCH is a rare disorder associated with a wide spectrum of presenting symptoms and variable clinical behavior and prognosis. Previously, the disease was separated into three classifications, including eosinophilic granuloma, Hand-Schüller-Christian and Letterer-Siwe (9). In 1990, a stratification system was adopted by the LCH Study Group that classified the disease into single system LCH and multisystem LCH (MS-LCH) (10). The former can be further divided into single site (unifocal bone, skin or lymph node) and multiple site (multifocal bone or lymph nodes) forms. MS-LCH is defined as having more than two organ systems involved at the time of diagnosis. In addition, MS-LCH can be subdivided into low-risk and high-risk forms. Low-risk patients have no involvement of high-risk organs, including the liver, lungs, spleen and hematopoietic system (11). However, high-risk patients have one or more of these organs involved (12). In the case of the present study, the patient presented with lungs and spleen involvement; thus, was classified in the high-risk group.

The diagnosis of LCH is based on histopathological examination of the biopsy specimens. Pathologically, LCH is characterized by multinucleated Langerhans' cells, histiocytes and eosinophils, although the hallmark cell is the Langerhans cell histiocyte. The gold standard for the diagnosis of the disease requires the presence of Birbeck granules on electron microscopy examination (13); however, in certain cases, immunohistochemistry can play a fundamental role in establishing a diagnosis. For example, a diagnosis can be established with the use of CD1a, S100 and/or CD45 immunostaining on histopathological specimens (14). Previously, a highly specific and sensitive monoclonal antibody against CD207 (langerin) has become commercially available. This protein appears to be important for the formation of the Birbeck-Broadbent granules (15-17). In the present study, a final diagnosis of LCH was confirmed based on the histopathological observations and immunohistochemical staining of the lesion cells with CD1a and S-100.

The etiology of LCH, which is characterized by a clonal proliferation of histiocyte-like cells, is controversial. There remains uncertainty regarding whether LCH is a neoplastic or inflammatory disorder. LCH has been described as a neoplastic process due to the monoclonal proliferation of Langerhans cells (18). However, there is also the possibility that LCH is a reactive inflammatory disorder resulting from a dysregulation of the immune system (18). Previously, a
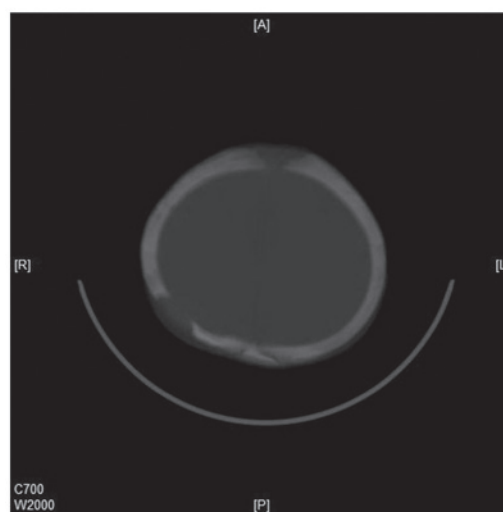

Figure 1. Computed tomography scan demonstrating a round-shaped osteolytic lesion of the right parietal bone.
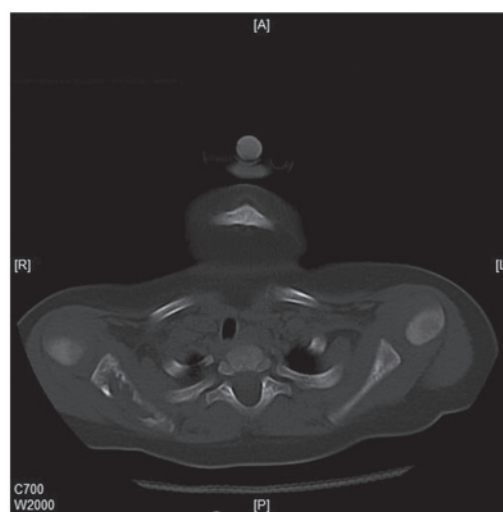

Figure 2. Computed tomography image showing osteolytic erosion of the right scapula.

Figure 3. A three-dimensional computed tomography image showing the osteolytic erosion of the right scapula.
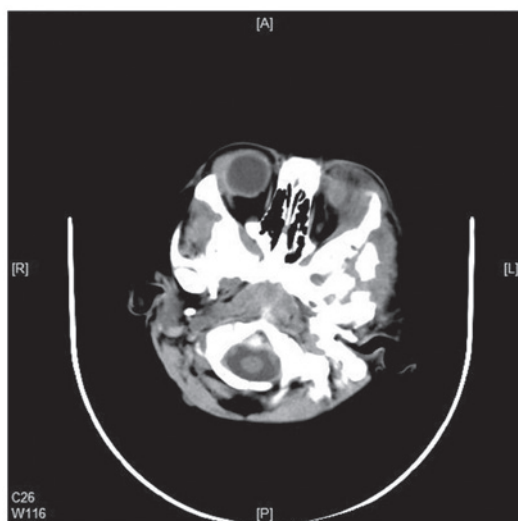
Figure 4. Computed tomography scan demonstrating the soft tissue mass in the left posterior orbit.
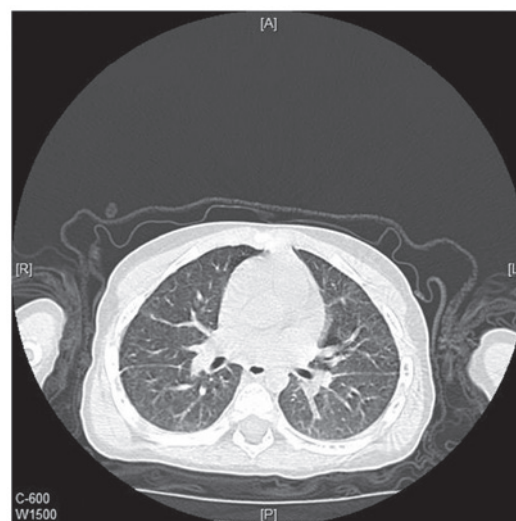

Figure 6. Computed tomography scan revealing increased interstitial markings in the lungs, with a number of markings showing a reticular pattern.
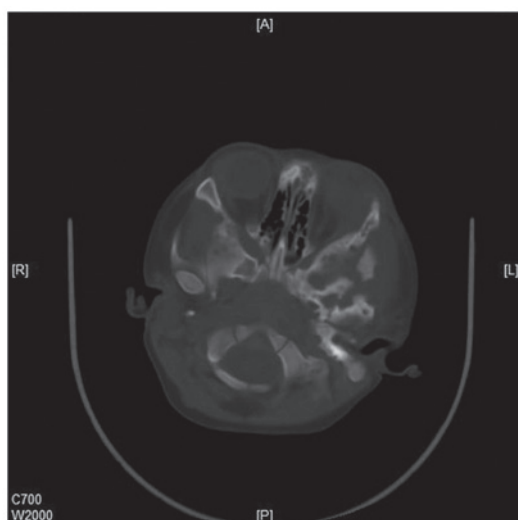

Figure 5. Computed tomography scan demonstrating the soft tissue mass in the left posterior orbit with bone erosion.

Figure 7. Computed tomography scan revealing the enlargement of the spleen.

number of findings with regard to the molecular aspects of the disease suggested the possibility that LCH may be the result of an immune dysregulation (10,19-21). For example, Langerhans cell histiocytes are known to release a number of inflammatory chemokines, including C-C chemokine receptor (CCR)1, CCR2, CCR5, CCR6, C-X-C chemokine receptor (CXCR)1, CXCR4, CCR7, chemokine (C-C motif) ligand (CCL)20/macrophage inflammatory protein (MIP)-3α, CCL2/ monocyte chemoattractant protein (MCP)-1, CCL3/MIP-1α, CCL4/MCP-4α, CCL5/RANTES, chemokine (C-X-C motif) ligand (CXCL8/interleukin (IL)-8 and CXCL10/IL-10. These chemokines are important for the recruitment of circulating immature dendritic cells, as well other immune cell types, such as T lymphocytes, macrophages and eosinophils. Subsequently, the recruited cells produce a number of additional cytokines, including IL-1, IL-3, IL-4, IL-5, IL-8, IL-10, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor-α, transforming growth factor-β

and leukemia inhibitory factor. This particular immunological setting, known as a 'cytokine storm', in which autocrine and paracrine stimulation is established among the cells, can explain a number of clinical symptoms, including fever and failure to thrive (22). By contrast, numerous genetic abnormalities, including the loss of heterozygosity, damage to the chromosomes and damage to genes (such as BRAF mutation), have been detected in LCH, which supports the possible clonal-expansive nature of the disease (22). These two pathways are currently under investigation with the aim to identify possible targets for the molecular therapy of LCH (10,14,15,19-21,23-27). One of the most exciting findings that may have therapeutical potential is the presence of the BRAF V600E mutation in LCH. Previous studies have demonstrated that BRAF V600E mutations are present in 50-60% of patients with LCH (27,28). The LCH patients with a BRAF V600E mutation respond to BRAF V600E inhibition. Haroche *et al* reported a treatment protocol using vemurafenib

(a BRAF inhibitor) in three patients with multisystemic and refractory Erdheim-Chester disease who carried the BRAF V600E mutation; two patients also had skin or lymph node LCH involvement. For all the patients, vemurafenib treatment resulted in a substantial and rapid clinical and biological improvement (29). However, more clinical trials are required to optimize the risk/benefit ratio of BRAF V600E inhibition in children.

Currently, the treatment for LCH with multisystem involvement is controversial. For patients with a multisystem disease, systemic multiagent chemotherapy is recommended. The most common chemotherapeutic agents are vinblastine, prednisone, etoposide and methotrexate, applied in various combinations (30). To date, a vinblastine- or etoposide-based regimen is most common for the treatment of LCH (31). However, severe and refractory LCH patients, particularly those with a life-threatening disease, may benefit from other therapies, including monoclonal antibodies that target CD1a, CD207 or CD52, specific cytokine inhibitors, 2-chlorode-oxyadenosine, BRAF V600E inhibition and bone marrow transplantation (28-32). In the present study, the patient was found to have a multivisceral form of the disease; thus, the VEP and VCP regimens were selected and applied for a year, after which the patient received vincristine therapy every two weeks for a year.

LCH is a rare proliferative disease of histiocyte-like cells that most commonly affects individuals in childhood. Diagnosis of LCH should be based on the synthetical analysis of clinical presentations, in addition to features of imaging and histopathology. Although certain cases regress spontaneously, other cases require systemic chemotherapy. The present study reported a rare infant case of LCH presenting with multisystem involvement, including that of the bone, skin, orbit, spleen and lungs. A vindesine- and prednisone-based regimen was selected for treatment and the patient was shown to progress well. However, the patient continues to undergo close follow-up to assess for signs of recurrence.

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