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Hemophagocytic Lymphohistiocytosis in Langerhans Cell Histiocytosis: A Case Report and Review of the Literature

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Summary: A toddler undergoing treatment for refractory Langerhans cell histiocytosis (LCH) developed concurrent hemophagocytic lymphohistiocytosis (HLH). These are thought to be distinct histiocytic disorders, with different pathophysiologies, diagnostic criteria, and treatments. HLH in a patient with LCH is thought to be quite rare. In this report, we review the presentation of our patient, as well as review the existing literature of other pediatric patients who have been diagnosed with both LCH and HLH.

Key Words: HLH, LCH, pediatric

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There are 3 distinct classes of histiocyte disorders: Langerhans cell histiocytosis (LCH), hemophagocytic lymphohistiocytosis (HLH) (and other rarer class II disorders), and malignant histiocytoses.[1] LCH is characterized by the proliferation of infiltrative Langerhans cells into skin or bone; multisystem disease can also involve the lungs, liver, spleen, bone marrow, and central nervous system. Although historically thought of as a benign, reactive process, *BRAF-V600E* mutations have been found in 25% to 70% of LCH patients, with *MAP2K1* positivity in 46% of BRAF-negative cases, raising the possibility that LCH is a malignancy.[2–4] Many believe LCH may represent a myeloid-lineage neoplasm driven by *ERK* signaling.[5,6] The treatment for LCH depends on the extent of disease and ranges from local and/or topical therapies to systemic chemotherapy.[5,7]

HLH is a disease of systemic, dysregulated immune activation and inflammation.[8] HLH can be familial or secondary to infections, autoimmune processes, or malignancies.[1] Treatment is with systemic dexamethasone and etoposide per the HLH94 protocol, with some patients, especially those with familial and/or reactivated HLH, ultimately requiring hematopoietic stem cell transplant for a cure.[9] Recent studies suggest that targeted therapies such as emapalumab may also play a role, especially in refractory cases.[10]

Table 1 reviews LCH and HLH in respect to presentation, diagnostic criteria, and treatments. Though they are regarded as separate disease states, they can occur together within the same patient. Favara et al[11] reviewed 30 pathology files of patients with coexisting LCH and macrophage activation; 7 of these met full diagnostic criteria for HLH. We report the case of a 20-month-old patient with multisystem LCH who developed HLH during treatment and summarize the literature for other case reports of HLH in LCH.

RESULTS: CASE DESCRIPTION

A 20-month-old male individual presented to his pediatrician with 6 months of progressive limp and unilateral leg pain, leading to a refusal to bear weight. He also had chronic drainage from bilateral ears. A radiograph showed a lucent, expansile lesion of the child's femur and biopsy was performed, showing $s100^+$, $CD1a^+$ LCH. Further evaluation using skeletal survey and positron emission tomography-computed tomography (PET/CT) revealed multiple bony lytic lesions of the skull, axial skeleton and extremities, a scaling diffuse rash of the scalp, and hypermetabolic cervical lymphadenopathy. He had no involvement of the lungs, liver, spleen, or bone marrow, and had normal magnetic resonance imaging appearance of his pituitary after passing a water deprivation test. His blood counts at diagnosis were normal other than a mild microcytic iron deficiency anemia. Liver function tests and ferritin were within normal limits. He began therapy with daily prednisone and weekly vinblastine as per the LCH-III protocol. After his initial 6 weeks of induction therapy, PET/CT showed improved but continued hypermetabolic bony lesions. He went on to the second phase of induction therapy with further improvement in lesions and then began continuation with pulses of prednisone and vinblastine every 3 weeks. Within 3 months, a follow-up PET/CT showed worsening hypermetabolic bony lesions. He was treated with cladribine for 5 days every 28 days. Interval imaging after 2 cycles again showed worsening hypermetabolic bony lesions, worsening skin rash on scalp, continued bilateral ear drainage, leg pain, and intermittent fevers with cough and rhinorrhea. He was found to be respiratory syncytial virus (RSV) positive at that time. The child began monotherapy with clofarabine 25 mg/m^2 daily for 5 days. Daily fevers continued for 2 weeks and he developed transaminitis with hypoalbuminemia and fluid overload. Blood cultures were negative, and he was empirically treated with broad-spectrum antibiotics secondary to neutropenia. CT scans done as part of fever evaluation revealed multiple new lytic skull lesions. Epstein-Barr virus (EBV) polymerase chain reaction was positive at 863 copies, which resolved without intervention over the next month. He met criteria for HLH with fevers, pancytopenia, ferritin >7500 ng/mL, triglycerides 526 mg/dL, soluble interleukin (IL)2 of 8191 U/mL, and hemophagocytosis in his bone marrow. Mutational analysis for *PRF1*, *MUNC 13-4*, *XIAP* and other common HLH-causing genes was normal. He thus began therapy via

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TABLE 1. Comparison of LCH and HLH[8,12]

	LCH	HLH
Pathophysiology	Derived from clonal CD1a$^+$ dendritic cells Lesions contain inflammatory infiltrates including high levels of T-cell regulatory molecules	Defects in target cell killing by cytotoxic T cells Immune dysregulation with excessive proinflammatory cytokine production and macrophage response Uncontrolled systemic inflammation Can be primary or secondary to an infection, malignancy, autoimmune condition
Molecular findings	38%-57% possess *BRAF-V600E* mutation	Perforin *MUNC 13-4*, *MUNC 18-2* *Syntaxin 11* *LYST*, *CHS1*, *Rab27A*, *AP3B1* *SH2D1A*, *XIAP*, *BIRC4*, *SAP*
Presenting signs/ symptoms	Bone pain, swelling, fractures Chest pain, cough, dyspnea Rash, seborrhea, otitis externa Polyuria, polydipsia Fatigue, weight loss, fevers, lymphadenopathy	Sepsis-like presentation Fever Cytopenias Hepatitis Splenomegaly Ataxia, seizures, abnormal MRI in 50%
Diagnostic criteria	Tissue biopsy containing CD207$^+$, CD1a$^+$ dendritic cells Characteristic morphology of Langerhans cells	Requires 5/8 diagnostic criteria: Fever Splenomegaly Cytopenias in ≥ 2 cell lines Hyperferritinemia > 500 mg/mL sIL2 > 2400 U/mL Hypertriglyceridemia/hypofibrinogenemia Hemophagocytosis in tissue biopsy Low or absent NK cell activity
Treatment	Local therapy for unifocal bony disease Prednisone, vinblastine Cladribine, cytarabine, clofarabine for refractory/ recurrent disease BMT for marrow/refractory disease	Decadron, etoposide ± cyclosporine Alemtuzumab for refractory cases Anti-INF-gamma antibodies for refractory cases

BMT indicates bone marrow transplant; HLH, hemophagocytic lymphohistiocytosis; IL2, soluble interleukin-2; INF, interferon; LCH, Langerhans cell histiocytosis; MRI, magnetic resonance imaging; NK, natural killer.

HLH94 with dexamethasone 10 mg/m^2/d and etoposide. At the end of the standard 8-week treatment period, his HLH was felt to be well controlled with resolution of fevers and cytopenias, as well as normalization of liver function tests, triglycerides, soluble IL2, and improvement in ferritin. He went on to complete an additional 5 cycles of clofarabine 25 mg/m^2 (6 total cycles), with end of therapy PET/CT showing no evidence of disease. He is now 3 years off therapy and doing very well.

DISCUSSION

Histiocytes or mononuclear phagocytes, the immune cells implicated in the pathogenesis of both LCH and HLH, serve many functions in the normal immune response. These include antigen presentation, activation of immune function through cytokine signaling, and phagocytosis.[12] In both LCH and HLH, affected tissues express high levels of T-cell stimulatory molecules and secrete inflammatory cytokines such as IL-6, interferon, and tumor necrosis factor.[8] Studies of LCH lesions suggest that chemokine receptors, including CCR6, maybe abnormally upregulated which contributes to tissue infiltration.[13,14] Furthermore, the T cells found abundantly in LCH lesions show increased expression for genes involved in leukocyte chemotaxis, such as SPP1, IL8 and plasminogen activator, among others.[15] A lesion with increased accumulation of histiocytes and T cells may thus be at increased risk of uncontrolled activation of these cells, resulting in hypercytokinemia and progressive organ dysfunction like that seen in HLH.[12] HLH has a known association with malignancy, especially leukemias and lymphomas. If LCH indeed represents a malignant clonal process of early myeloid-lineage cells, this may also explain the potential association between the 2 entities. Alternatively, it could be that children with LCH who require multiagent or prolonged chemotherapy courses develop HLH secondary to immune dysregulation from the treatments rather than the underlying disease.

HLH in LCH is thought to be a rare phenomenon and we aimed to summarize the available reports (Table 2). In our patient (patient 8), and in those reported throughout the literature, common findings included young age, multisystem LCH, history of systemic chemotherapy, and often concurrent infection. Our patient with multisystem LCH had received a prolonged course of multiagent chemotherapy secondary to his refractory disease and then developed RSV. He was also positive for EBV. Although we did not find any other reports of RSV-associated HLH, EBV is a well-known trigger of HLH, as are other viruses including influenza, parvovirus, etc. One evaluation of 182 pediatric patients with EBV who also met criteria for HLH, showed significant immune dysregulation. These patients had abnormal natural killer cell activity, as well as decreased CD4$^+$ T cells, and a decreased ratio of CD4$^+$/CD8$^+$ T cells, resulting in increased T-cell activation and decreased inhibition. HLA-DR expression was elevated, indicating high levels of T-cell activation, and further downstream cytokines such as IL2 and interferon-gamma were also significantly elevated.[16] Thus, viral infections including EBV can result in uncontrolled proliferation and activation of T

TABLE 2. Reported Patients With LCH and HLH

	Patient 1[11]	Patient 2[11]	Patient 3[18]	Patient 4[19]	Patient 5[20]	Patient 6[21]	Patient 7[22]	Patient 8
Age at HLH	10 mo	17 mo	3 y	2 y	10 mo	3 y	1 y	2 y
Areas of LCH	Colon, skin, ln, bone marrow	Left mastoid	Skin, bone, ln, bone marrow	Skin, bone	Skin, bone, ln, lungs	Skin, bone, ln	Skin, bone, ln, hepatomegaly	Skin, bone
Prior therapies	None	None	2CDA, ARAC×6 mo	Prednisone, VBL, 6-MP, MTX×6 mo	None	Prednisone, VBL, 6-MP, MTX	Prednisone, VCR, ARAC	Prednisone, VBL, 2CDA
Clinical course	Presented with fever, diarrhea, HSM, LAD, and pulmonary disease	Presented with fever, HSM, LAD, and bone lesion	2 cycles of clofarabine. Lesions improved but developed HLH	Presented with HLH on 3 different occasions 2 to 6 mo apart in the setting of influenza, HSV, and adenovirus	Presented with HLH and CMV. Diagnosed with HLH and LCH of skin	9 mo after therapy completed, the patient presented with HLH	3 wk into therapy for LCH, the patient developed HLH	7 d after beginning clofarabine therapy, developed HLH. EBV PCR+
HLH treatment	Chemotherapy	Prednisone, VBL, VCR	Dexamethasone, etoposide	Cessation of chemotherapy, antibiotics, antivirals, IVIG	Prednisone, etoposide	Dexamethasone, cyclo A	Dexamethasone, etoposide, cyclo A, followed by flu, mel, ATG cytox, and UCBT	Dexamethasone, etoposide
Outcome	Died 10 mo after diagnosis	CR	Continued disease progression, followed by death within 2 mo	CR	CR	CR	CR and engrafted	Disease-free now 3 y off therapy

ARAC indicates cytarabine; ATG, anti-thymocyte globulin; 2CDA, cladribine; CMV, cytomegalovirus; CR, complete remission; cytox, cyclophosphamide; EBV, Epstein-Barr virus; flu, fludarabine; HLH, hemophagocytic lymphohistiocytosis; HSM, hepatosplenomegaly; IN, lymph node; IVIG, intravenous immunoglobulin; LAD, lymphadenopathy; LCH, Langerhans cell histiocytosis; mel, melphalan; MP, mercaptopurine; MTX, methotrexate; PCR, polymerase chain reaction; UCBT, unrelated cord blood transplant; VBL, vinblastine; VCR, vincristine.

cells, which may be further increased in patients with pre-existing immune dysregulation from chemotherapy and/or the underlying disease state. We believe the combination of immunosuppression and infection may have led to HLH in our patients. Interestingly, like our patient, another reported patient with LCH also developed HLH while receiving clofarabine, a deoxyadenosine analog. Although this may be coincidence, clofarabine after multiple other immunosuppressive agents may have contributed to significant immune dysregulation and HLH in these patients. A recently published multicenter article reviewed 29 patients who met criteria for HLH and LCH. As in the patients reviewed in Table 2, about half of the patients met criteria for HLH at or around the diagnosis of LCH. Most had active LCH at diagnosis of HLH and were receiving treatments similar to those listed in Table 2. Overall, 31% had some kind of infection when HLH developed, including EBV. HLH was increased most in those with risk organ involvement, but also seen in young females without bony involvement. The combination of HLH and LCH was associated with a poor prognosis.[17] Taken together, it appears HLH in LCH is not as unusual as originally thought. Since these diagnoses share common histologic and diagnostic findings but require different treatment strategies, knowledge of their potential relationship, and which patients are at highest risk, is critical to timely diagnosis and treatment.

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