World Journal of Pediatrics (2019) 15:536–545
https://doi.org/10.1007/s12519-019-00304-9

REVIEW ARTICLE

Childhood Langerhans cell histiocytosis: a disease with many faces

Alexander K. C. Leung[1] · **Joseph M. Lam**[2,3] · **Kin Fon Leong**[4]

Received: 2 July 2019 / Accepted: 1 August 2019 / Published online: 28 August 2019

Abstract

Background Langerhans cell histiocytosis (LCH) is a group of diseases characterized by the proliferation and accumulation of Langerhans cells. Clinical presentations of LCH vary widely.

Data sources A PubMed search was conducted using Clinical Queries with the key term "Langerhans cell histiocytosis". The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, and reviews. This paper is based on, but not limited to, the search results.

Results Generally, patients with LCH can be divided into two groups based on the extent of involvement at diagnosis, namely, single-system LCH and multisystem LCH. The involvement may be unifocal or multifocal. Patients with isolated bone lesions typically present between 5 and 15 years of age, whereas those with multisystem LCH tend to present before 5 years of age. The clinical spectrum is broad, ranging from an asymptomatic isolated skin or bone lesion to a life-threatening multisystem condition. Clinical manifestations include, among others, "punched out" lytic bone lesion, seborrheic dermatitis-like eruption, erythematous/reddish-brown crusted/scaly papules/maculopapules/plaques/patches, and eczematous lesions, diabetes insipidus, hepatosplenomegaly, cytopenias, lymphadenopathy, and an acute fulminant disseminated multisystem condition presenting with fever, skin rash, anemia, thrombocytopenia, lymphadenopathy, and hepatosplenomegaly. The diagnosis is clinicopathologic, based on typical clinical findings and histologic/immunohistochemical examination of a biopsy of lesional tissue. Positive CD1a, S100, and/or CD207 (Langerin) immunohistochemical staining of lesional cells is required for a definitive diagnosis. Watchful waiting is recommended for patients with skin-only LCH. Patients with symptomatic or refractory skin-only LCH may be treated with topical tacrolimus/corticosteroids, topical nitrogen mustard, oral methotrexate, or oral hydroxyurea. The current recommended first-line therapy for patients with multisystem LCH is 12 months therapy with prednisone and vinblastine. Mercaptopurine is added for patients with risk organ involvements.

Conclusions Because of the broad spectrum of clinical manifestations and the extreme diversity of disease, LCH remains a diagnostic dilemma. Morphological identification of LCH cells and positive immunochemical staining with CD1a, S100, and/or CD207 (Langerin) of lesional cells are necessary for a definitive diagnosis.

Keywords Cytopenia · Diabetes insipidus · Eczematous lesions · Hepatosplenomegaly · Lymphadenopathy · Seborrheic dermatitis-like eruption

Introduction

Langerhans cell histiocytosis (LCH) is a group of diseases with various clinical manifestations characterized by the proliferation and excess accumulation in a variety of organs of Langerhans cells derived from myeloid progenitor cells from the bone marrow [1, 2]. The disease can be localized in a single organ or systemic with multi-organ involvement [3]. Langerhans cells are specialized dendritic cells found in the epidermis; these cells were first recognized by Paul Langerhans in 1868 [4]. The term "LCH" is generally preferred to the older term "histiocytosis X" [5–7]. The term "histiocytosis X" was coined by Lichtenstein to describe

✉ Alexander K. C. Leung
aleung@ucalgary.ca

[1] Department of Pediatrics, The University of Calgary, and The Alberta Children's Hospital, #200, 233, 16th Avenue NW, Calgary, AB T2M 0H5, Canada

[2] Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada

[3] Department of Dermatology and Skin Sciences, University of British Columbia, Vancouver, BC, Canada

[4] Pediatric Institute, Kuala Lumpur General Hospital, Kuala Lumpur, Malaysia

three related syndromes, namely, eosinophilic granuloma (unifocal LCH with a solitary or few lytic bone lesions), Hand–Schüller–Christian disease (multifocal LCH with classic triads of exophthalmos, diabetes insipidus, and lytic bone lesions), and Letterer–Siwe disease (fulminant and disseminated LCH) [5–7]. The purpose of this communication is to familiarize readers with the clinical manifestations, diagnosis, and management of LCH.

A PubMed search was conducted in May 2019 using Clinical Queries with the key term "Langerhans cell histiocytosis". The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, and reviews. Discussion is based on, but not limited to, the search results.

Epidemiology

The estimated incidence of LCH ranges from 2 to 9 cases per million children younger than 15 years of age per year [1, 8–11]. The peak incidence is between 1 and 3 years of age [7, 12–14]. Five to ten percent of the patients have disease onset at birth or shortly thereafter [15]. Although LCH can occur at any age, it is very rare in adults [16]. Pulmonary LCH is a rare disorder occurring mainly in adult smokers, but it is not part of the spectrum of the disease in children. The male-to-female ratio is about 2.5:1 [17]. The incidence is higher in Hispanics than in blacks and non-Hispanic whites [7, 18]. Familial clustering of LCH has been reported [14, 19, 20]. The concordance rate is higher in monozygotic twins than in dizygotic twins, suggesting genetic predisposition in at least some cases [19, 20].

Pathogenesis

The exact pathogenesis is not known. It has been debated for years whether LCH is reactive or neoplastic in nature [9]. Arguments in favor of a reactive nature of LCH include occasional spontaneous remissions of LCH lesions, as well as prominent inflammatory infiltrates and massive production of multiple cytokines in LCH lesions [9, 21, 22]. Thus far, there are no epidemiologic data to support an environmental or infectious cause for LCH [9, 21, 22].

On the other hand, clonal proliferation of LCH cells within LCH lesions, mutations with hematopoietic precursors, somatic activating gene mutations in the nitrogen-activated protein kinase (MAPK) pathway, fatal outcome, and response to chemotherapy are in favor of a neoplastic cause of the disease [1, 5, 21–25]. In this regard, LCH cells share surface markers with CD1a+/CD207+ myeloid dendritic cells [5, 9, 26]. Somatic activating gene mutations in the MAPK pathway are detectable in a significant number of patients with LCH [7, 27, 28]. The genes in the MAPK pathway are more frequently mutated in human malignancy [29]. Oncogenic *BRAF* V600 E mutation is found in 50–60% of patients with LCH; such mutation renders the MAPK pathway constitutionally active [1, 3, 5, 7, 8, 29]. Other *BRAF* mutations include in-frame deletions, duplications, and fusions [5]. It should be noted that *BRAF* mutations are not specific for LCH, because *BRAF* mutations can also be seen in patients with hairy cell leukemia, melanoma, lung cancer, etc. Approximately 10–25% of patients with LCH have mutations in the *MAP2K1* gene [1, 3]. Mutations in *ARAF*, *ERBB3*, *NRAS*, and *KRAS* have also been reported in patients with LCH but at lower rates [1, 3, 5, 29].

Histopathology

Histopathologic findings include an inflammatory infiltrate of eosinophils, T lymphocytes, neutrophils, macrophages, multi-nucleated giant cells, and LCH cells [7, 17, 30, 31]. LCH cells are large (10–15 μm in diameter), oval, and mononuclear, with a folded nucleus ("coffee bean", "twisted towel" or "kidney-shaped" appearance), a discrete nucleolus, and homogeneous eosinophilic cytoplasm [13, 24, 26, 30, 32]. The LCH cells resemble cutaneous Langerhans cells except that LCH cells are not dendritic [7, 26]. These cells express the histiocytic markers CD1a, S100, and CD207 (Langerin) and contain Birbeck granules [7]. The cytoplasmic tennis racquet-shaped Birbeck granules can be visualized on electron microscopy [17, 24, 25, 32, 33]. Using specific fluorescently tagged antibodies, LCH cells stain positive for CD1a, S100, and CD207 (Langerin) which are transmembrane proteins expressed in LCH lesions [17, 30]. Langerin is a cell surface receptor that induces the formation of Birbeck granules [24].

Clinical classifications

Generally, patients with LCH can be divided into two groups based on the extent of involvement at diagnosis, namely, single-system LCH and multisystem LCH (Table 1) [7, 34, 35]. In single-system LCH, only one organ or system is involved such as bone, skin, lymph node (not the draining lymph node of another LCH location), lungs, central nervous system, or others such as thyroid or thymus [34, 35]. The involvement may be unifocal (single lesion on bone or lymph node) or multifocal (multiple lesions on bone or multiple lymph nodes) [7, 34–36]. In multisystem LCH, two or more organs or systems are involved at diagnosis, with or without involvement of risk organs (spleen, liver, and/or bone marrow) [7, 10, 34, 35]. The distinction between single-system

Table 1 Clinical classifications of Langerhans cell histiocytosis

A. Single-system Langerhans cell histiocytosis (only one organ or system is involved at diagnosis)
1. Unifocal (single lesion on bone or lymph node[a])
2. Multifocal (multiple lesions on bone or multiple lymph nodes)
B. Multisystem Langerhans cell histiocytosis (two or more organs or systems are involved at diagnosis)

[a]Not the draining lymph node of another Langerhans cell histiocytosis location

LCH and multisystem LCH is essential both for treatment and prognosis [30].

Clinical manifestations

In general, patients with isolated bone lesions typically present between 5 and 15 years of age whereas those with multisystem LCH tend to present before 5 years of age [9, 13, 17]. Skin involvement predominates in multisystem LCH in children under the age of 1 year [37]. In this regard, acute disseminated multisystem LCH is most commonly seen in children under 2 years [7].

Clinical manifestations vary depending on the sites and extent of involvement [29]. The clinical spectrum is broad, ranging from an asymptomatic isolated skin or bone lesion to an acute, disseminated, fulminant, life-threatening, multisystem condition presenting with fever, skin rash, anemia, thrombocytopenia, lymphadenopathy, and hepatosplenomegaly [13, 14]. Sites of involvement, in order of decreasing frequency, include the bone (79%), skin (36%), pituitary gland (25%), liver (16%), bone marrow (15%), spleen (14%), lymph nodes (13%), lungs (13%), and central nervous system (5%) [3, 7]. The kidneys and gonads are usually spared [31, 37].

Bone

Bone is the most common system affected [3, 7]. Unifocal involvement is more common than multifocal involvement [6]. The most common site of involvement is the skull, followed by the spine, extremities, pelvis, and ribs [17, 24]. The hands and feet are often spared [3, 37]. Although some bone lesions are asymptomatic, pain and a soft raised mass in a localized area of the bone are common [2, 9, 26]. Other symptoms include dull aching pain, inability to bear weight, and limited range of movement [38]. Typical radiographic findings include a solitary "punched out" lytic lesion of the skull, symmetrical flattening of the anterior and middle vertebral column ("vertebra plana"), and endosteal scalloping of the long bones [6, 17, 39].

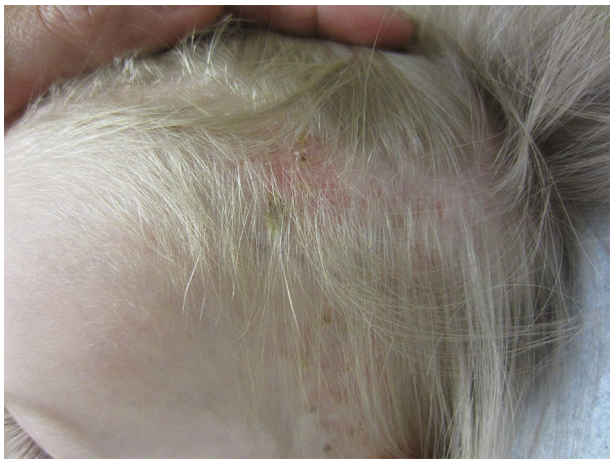

Fig. 1 Seborrheic dermatitis-like eruption on the scalp presenting as slightly elevated papules covered by yellow-brown scales

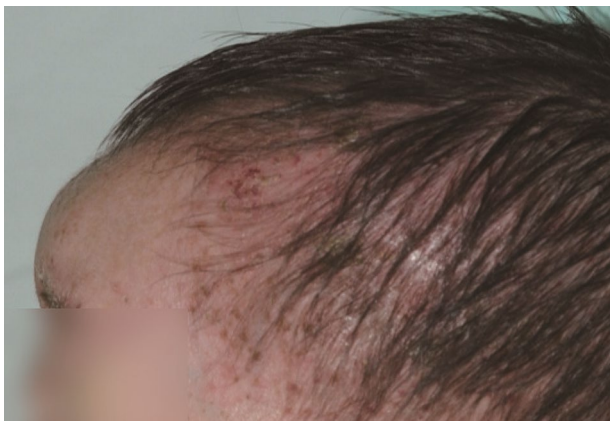

Fig. 2 Erythematous scaly papules over the scalp

Skin

Although cutaneous manifestations are less common than bone manifestations, they are the first manifestation in approximately 80% of cases and are often the leading clue for disease diagnosis [11, 16]. Common cutaneous manifestations include a seborrheic dermatitis-like eruption (Fig. 1), erythematous/reddish-brown crusted/scaly papules/maculopapules/plaques/patches and eczematous lesions (Figs. 2, 3) [9, 11, 13, 23, 30, 36, 40]. Sites of predilection include the scalp, abdomen, chest, back, and intertriginous areas [3]. Lesions tend to be more severe in intertriginous areas which may become ulcerated [9, 37]. Other cutaneous manifestations include petechiae/purpura [40], hypopigmented macules/papules [40], umbilicated (molluscum-like) papules, vesicles/blisters/bullae, pustules, nodules, and blueberry muffin spots [9, 11, 36, 41–44]. Gingival hypertrophy, mucosal ulcers, and intraoral masses may also occur [7, 9,

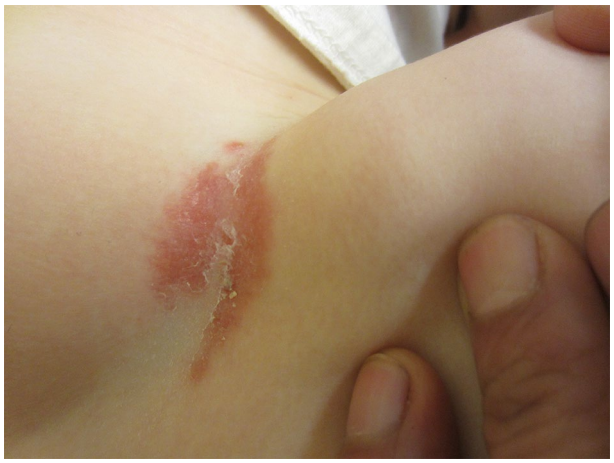

Fig. 3 Erosive erythematous plaque over the left inguinal area

45, 46]. Nail involvement is relatively rare and may manifest as subungual hyperkeratosis/pustules/purpura, paronychial erythema, longitudinal grooving, onychauxis, and onycholysis [32, 47, 48].

Congenital self-healing LCH (also known as Hashimoto–Pritzker disease), a skin-only LCH, typically presents at or shortly after birth as asymptomatic multiple, or less commonly, solitary, red to brown papules or nodules that are often crusted or ulcerated [49–52]. Although the lesion can be present anywhere on the body, it appears most commonly on an extremity [2, 51]. Solitary congenital self-healing LCH appears to be isolated without systemic involvement [2]. Typically, the solitary papule/nodule resolves spontaneously within a few weeks to months, occasionally, leaving a residual hyper- or hypopigmented macule or scar [2, 51, 53–55].

Hypothalamic–pituitary axis

Antidiuretic hormone (arginine vasopressin) is synthesized in the hypothalamus and transported as neurosecretory vesicles to the posterior pituitary gland. Central (neurogenic) diabetes insipidus is the most common endocrine manifestation in LCH and may result when the hypothalamic–pituitary axis is involved with consequent impairment of antidiuretic hormone secretion from the posterior pituitary gland [16, 45, 56–58]. The condition typically presents with polydipsia, polyuria, and nocturia [7]. Approximately 50% of patients with central diabetes insipidus develop deficiency of anterior pituitary hormones (such as growth hormone, thyroid-stimulating hormone, adrenocorticotropic hormone, luteinizing hormone, and follicle-stimulating hormone) with resultant growth failure, hypothyroidism, hyperprolactinemia, hypoadrenalism, hypogonadism, amenorrhea, and precocious or delayed puberty [24, 31, 45, 56]. Non-endocrine hypothalamic dysfunction may present with eating disorders, obesity, sleeping disorders, fatigability, temperature instability, and autonomic disturbance [24, 31].

Liver and spleen

Involvement of the liver and/or spleen may result in hepatomegaly and/or splenomegaly. Patients with hepatic dysfunction may present with elevated liver enzymes, jaundice, hypoalbuminemia, edema, ascites, and clotting factor deficiencies [7, 9, 26, 59].

Bone marrow

Hematopoietic involvement may result in anemia, leucopenia, and/or thrombocytopenia. Anemia may present with pallor, easy fatigability, anorexia, dizziness, and irritability [60]. Patients with leukopenia may present with recurrent infection, whereas patients with thrombocytopenia may present with bleeding diathesis.

Lymph nodes

Lymph nodes involvement occurs in approximately 13% of patients with LCH [3, 7]. Cervical lymph nodes are most commonly involved, but axillary, inguinal, mediastinal, and retroperitoneal lymph nodes can also be involved [38]. Lymph nodes draining involved skin or bone are more commonly affected [37]. Affected lymph nodes are usually matted; the consistency may be soft, firm, or hard [9].

Lungs

Lungs involvement is less frequent in children than adults in whom smoking is a significant risk factor [7, 9]. Patients with lung involvement may present with non-productive cough, dyspnea, tachypnea, chest pain, and constitutional symptoms such as malaise, fatigability, weight loss, and fever [7, 9]. Although the lung was once believed to be a risk organ, recent studies have suggested it to be otherwise [7].

Central nervous system

Involvement of the central nervous system occurs in approximately 5% of patients with LCH [3]. Involvement of the ethmoid, orbital, temporal, or zygomatic bones confers a higher (25%) chance of central nervous system involvement [7, 26]. Central diabetes insipidus caused by involvement of the pituitary gland occurs in approximately 25% of patients overall [26, 31]. Depending on the site of the

space-occupying lesion, other clinical manifestations include headache, dizziness, vomiting, diplopia, ataxia, change in mental status, personality change, and seizures.

Diagnosis and differential diagnosis

The diagnosis is clinicopathologic, based on typical clinical findings and histologic/immunohistochemical examination of a biopsy of lesional tissue [31, 34]. The biopsy should be taken from the most accessible organ: skin in the majority of cases, followed by an osteolytic bone lesion [34]. Positive CD1a, S100, and/or CD207 (Langerin) immunohistochemical staining of lesional cells is required for a definitive diagnosis [26, 33–35]. Electron microscopy for the detection of Birbeck granules is no longer needed because expression of Langerin has 100% concordance with the ultrastructural presence of Birbeck granules [33–35].

Laboratory and radiographic evaluation

The following laboratory tests are generally recommended, namely, complete blood cell count with differential, C-reactive protein, serum electrolytes, serum creatinine, liver function tests [e.g., serum albumin, total protein, bilirubin, glutamic pyruvic transaminase (SGPT), glutamic oxaloacetic transaminase (SGOT), gamma glutamyl transferase (γGT), alkaline phosphatase], coagulation studies [e.g., prothrombin time (PT), international normalized ratio (INR)], and *BRAF* V600E testing [33–35, 61]. Performing *BRAF* mutation analysis in all patients with suspected LCH is now the standard of care [61]. Unfortunately, *BRAF* mutation analysis is not universally available. Radiographic imaging tests include radiography of the chest, skeletal radiograph survey and abdominal ultrasound (especially for young children) [25, 30, 34, 35]. Certain scenarios may require additional testing. For example, a bone marrow aspiration and biopsy are indicated in patients with multisystem involvement presenting with pancytopenia to rule out other causes of bone marrow failure [30, 38]. An early morning urine specimen for specific gravity and osmolality and a water deprivation test should be ordered if diabetes insipidus is suspected [38]. A full endocrine workup should be performed for patients with pituitary dysfunction [38]. A cranial magnetic resonance imaging (MRI) or computerized tomography (CT) scan should be considered for patients with pituitary dysfunction, neurologic symptoms, or skull lesions [25, 34].

Differential diagnosis

As LCH can affect almost every organ, the differential diagnoses are extensive. The differential diagnoses of some common manifestations of LCH are listed in Table 2 [7, 30, 33–35, 40, 62–89].

Complications

Generally, major complications occur in approximately 50% of patients with LCH [25]. Because of the disease per se and its complications, LCH has an adverse effect on quality of life [90]. Complications of bone involvement include pathological fracture (long bone and/or vertebra involvement), scoliosis/spinal paralysis (spinal involvement), visual loss/exophthalmos (orbital involvement), palatal perforation (maxilla involvement), otorrhea/hearing loss (temporal bone/mastoid involvement), "loose teeth syndrome"/loss of teeth (jaw involvement), cranial nerve palsies (skull involvement), and torticollis (odontoid involvement) [9, 13, 14, 24, 37, 38, 87].

Skin lesions can be cosmetically unsightly and socially embarrassing. Unfamiliarity of the skin lesions of LCH can lead to misdiagnosis and maltreatment, which is usually the case.

Involvement of the hypothalamic–pituitary axis may result in central diabetes insipidus, deficiencies of hormones secreted by the anterior pituitary gland, and hypothalamic dysfunction (vide supra) [24, 31, 36, 87]. Complications resulting from the deficiencies of hormones secreted by the pituitary gland, especially if prolonged and severe, include dehydration (antidiuretic hormone deficiency), short stature/growth failure (growth hormone deficiency), hypomentality (thyroid-stimulating hormone deficiency if occurring early in life), adrenal crisis (adrenocorticotropic hormone deficiency) and subfertility/infertility (luteinizing hormone/follicle-stimulating hormone deficiency) [91].

Complications of hepatic involvement include sclerosing cholangitis and cirrhosis of liver; the differentiation between sclerosing cholangitis and cirrhosis of liver can be very difficult [7, 9, 26]. Patients with massive splenomegaly are at risk for hypersplenism with resultant thrombocytopenia, splenic rupture, and respiratory compromise [7, 26, 45]. Both liver and spleen are "risk organs" and their involvement denotes a poor prognosis [7, 26].

Bone marrow is also a "risk organ". As such, bone marrow involvement is associated with a poor prognosis [26]. Most patients with bone marrow involvement are young children with multisystem LCH [7]. Severe bone marrow involvement is often associated with secondary hemophagocytosis followed by a fatal course [24, 31].

Superficial lymph node involvement is relatively harmless. On the other hand, massive lymph node enlargement in the mediastinum may cause superior vena cava syndrome and compression of the airway with resultant respiratory distress [9].

Table 2 Differential diagnoses of some common manifestations of LCH

Manifestations	Differential diagnoses
Dermatosis	Seborrheic dermatitis [62–64] Atopic dermatitis [30, 34] Erythema toxicum [34, 35] Monilial diaper dermatitis [62] Irritant diaper dermatitis [30] Intertrigo [30] Dermatophytosis [30] Herpes simplex [30] Varicella [30] Scabies [35, 65] Psoriasis [66] Lichen planus [67] Lichen nitidus [40, 68] Molluscum contagiosum [42, 43, 69, 70] Neonatal hemangiomatosis [71–73] Juvenile xanthogranuloma [7, 33] Mastocytosis [74] Malignant melanoma [75]
Lytic bone lesion	Osteomyelitis [76] Osteogenic sarcoma [34, 35] Ewing sarcoma [34, 35] Multiple myeloma [7, 76] Bone metastasis [76] Non-ossifying fibroma [76] Giant cell tumor [76] Enchondroma [76] Simple (unicameral) bone cyst [76] Aneurysmal bone cyst [34, 35] Fibrous dysplasia [76]
Central diabetes insipidus	Nephrogenic diabetes insipidus [77] Diabetes mellitus [77] Primary polydipsia [77]
Hepatosplenomegaly	Infections (e.g., infectious mononucleosis, malaria, leishmaniasis, congenital syphilis) [78, 79] Chronic liver disorders (e.g., chronic active hepatitis, cirrhosis) Congestive heart failure Malignancies (e.g., leukemia, lymphoma) [80] Hematological disorders (e.g., thalassemia, myelofibrosis) [80] Storage disorders (e.g., glycogen storage disease, Niemann–Pick disease, Gaucher disease) [80] Systemic lupus erythematosus Sarcoidosis
Cytopenias	Aplastic anemia [81, 82] Fulminant sepsis [82] Malignancies (e.g., aleukemic leukemia, metastatic cancer infiltrating the bone marrow) [82] Myelodysplastic syndrome [81, 82] Medications (e.g., cytotoxic drugs, idiosyncratic reactions to medications) [81] Autoimmune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis) [81] Disseminated intravascular coagulopathy [81] Hypersplenism [82] Hemophagocytic lymphohistiocytosis [82] Syndromes (e.g., Fanconi syndrome, Wiskott–Aldrich syndrome, Shwachman–Diamond syndrome) [82]

Table 2 (continued)

Manifestations	Differential diagnoses
Cervical lymphadenopathy	Viral infections (e.g., infectious mononucleosis, rubella, rubeola, HIV) [78, 83, 84] Bacterial infections (e.g., streptococcal pharyngitis, cat scratch disease, tuberculosis) [85] Protozoal infections (e.g., toxoplasmosis, leishmaniasis) [86] Fungal infections (e.g., candidiasis, histoplasmosis) [86] Malignancies (e.g., lymphoma, leukemia, metastasis) [86–88] Kawasaki disease [89] Rosai–Dorfman disease [7] Kikuchi–Fujimoto disease [86] Sarcoidosis [30] Collagen vascular diseases [86] Serum sickness [86] Medications (e.g., phenytoin, carbamazepine, hydralazine) [86]

Patients with lung involvement are at risk for pneumothorax, pleural effusion, pulmonary fibrosis, and pulmonary hypertension [7, 9, 24].

Neurodegeneration of the central nervous system, a progressive and devastating complication, occurs in 1–3% of patients with LCH [9]. It is believed that the neurodegeneration is due to demyelination and gliosis from cytokine/chemokine-mediated neural damage [31, 37]. Clinically, neurodegeneration of the central nervous system manifests as headaches, dysarthria, visual disturbances, cerebellar dysfunction, psychomotor developmental delay, neuropsychologic deficits, and behavioral problems [9, 31].

It has been shown that adult patients with LCH are at risk of malignancies such as Hodgkin lymphoma, lymphoblastic leukemia, and solid tumors [25, 92, 93].

Management

Treatment depends on the site and extent of the disease. Patients with LCH will benefit from a multidisciplinary approach. Consultations with a dermatologist, oncologist, orthopedic surgeon, endocrinologist, hematologist, and neurologist should be considered.

Single-system LCH

Watchful waiting is recommended for patients with skin-only LCH [29, 45, 90]. In the majority of cases, isolated skin lesions regress spontaneously, especially for those with congenital self-healing LCH [2, 52]. Children with isolated skin lesions, however, should be followed up closely, because a significant number of them will progress to multisystem LCH [7, 29]. Patients with symptomatic or refractory skin-only LCH may be treated with topical tacrolimus/corticosteroids, topical nitrogen mustard, oral methotrexate, oral hydroxyurea, oral thalidomide, or psoralen and ultraviolet A therapy [29, 45, 61].

A solitary lesion in the frontal, parietal, or occipital bone (non-CNS risk) may be treated with curettage with or without an intralesional corticosteroid injection [9, 29, 61]. On the other hand, a solitary lesion in the mastoid, orbital, temporal, or sphenoid bone (CNS risk) may require combined treatment of oral prednisone and intravenous vinblastine [29, 45, 61]. Spinal or femoral bone lesion may benefit from radiation therapy and bracing [45, 61].

For single lymph node involvement, surgical excision is the treatment of choice [61]. If there are two or more regional lymph nodes involved, treatment consists of a short course of systemic corticosteroids. Treatment-resistant lymph nodes may require chemotherapy as given for multisystem LCH [61].

Multisystem LCH

The current recommended first-line therapy for patients with multisystem LCH is 12 months therapy with prednisone and vinblastine [3, 29, 30, 61, 94]. The regimen consists of 6 weeks of initial therapy with prednisolone (40 mg/m^2/day orally for 4 weeks, and then tapered over 2 weeks) and vinblastine (6 mg/ m^2 weekly intravenous bolus for 6 weeks) [61]. This is followed by a continuation therapy for a total treatment duration of 12 months [61, 94]. Continuation therapy consists of prednisolone (40 mg/m^2/day) given orally for 5 days and vinblastine (6 mg/m^2) as an intravenous bolus every 3 weeks [94]. Mercaptopurine (50 mg/mg/m^2/day given orally) is added for patients with risk organ involvement [30, 61]. Treatment of lesions in the central nervous system can be difficult because of poor penetration of chemotherapeutic agents into the central nervous system and the risk of neurodegenerative complications which might occur.

Patients who do not respond to standard first-line therapy may either undergo a second induction phase (for those without risk organ involvement) or proceed to second-line therapy (for those with risk organ involvement) [61]. Cytarabine (100–170 mg/m^2/day for 3–5 days every 3–4 weeks) can be used for second-line therapy [61].

Targeted therapy

Vemurafenib, a *BRAF* V6000 inhibitor, may be considered for the subset of high-risk patients with *BRAF* V6000 mutations [9, 30, 45]. Likewise, trametinib and cobimetinib, MEK inhibitors, may be considered for high-risk patients with mutations in the MAPK pathway [29, 30]. Currently, the use of target therapy is still experimental and should only be used judiciously as an additional tool rather than as a replacement therapy [29]. The optimal dose, time, and duration of treatment have yet to be determined.

Additional therapy

It goes without saying that complications such as diabetes insipidus, short stature, hypothyroidism, hypoadrenalism, and hypogonadism may require treatment with appropriate hormones. Hearing loss and musculoskeletal disabilities should be properly treated. Patients with LCH need to have long-term follow-up to monitor for disease recurrence and late effects [61].

Prognosis

Prognosis is dependent on a variety of factors, including the age of onset, the rate of disease progression, the number of organs involved, and the degree of organ dysfunction [12, 16, 33, 38, 39]. Sequelae from LCH are common, affecting more than 50% of patients [95]. In general, children with single-system involvement (single system LCH) tend to have more favorable outcomes than those with multisystem involvement (multisystem LCH) at diagnosis, with or without involvement of "risk organs" [9, 11]. The mortality rate is very low for patients with single-system LCH, whereas the mortality rate ranges from 10 to 50% for those with multisystem system LCH [24, 94]. The prognosis is the worst in children under the age of 2 years with disseminated multisystem system LCH and organ dysfunction [25, 33, 38, 39]. When LCH is localized to the bone or skin, the lesion may spontaneously resolve in few months or years [24, 96]. Congenital self-healing LCH has the best prognosis, as skin lesions tend to spontaneously resolve within months [31, 51, 52].

Conclusions

Because of the many faces of the disease, LCH remains a diagnostic dilemma for the treating physician. Familiarity with wide variation in clinical manifestation of LCH is important which may give clues to the diagnosis. Morphological identification of LCH cells and positive immunochemical staining with CD1a, S100, and/or CD207 (Langerin) of lesional cells are necessary for a definitive diagnosis.

Author contributions AKCL wrote the first draft of the manuscript, as well as a statement of whether an honorarium, grant, or other form of payment was given to anyone to produce the manuscript. JML and KFL contributed to drafting and revising the manuscript. All authors have seen and approved the final version submitted for publication and take full responsibility for the manuscript.

Funding There is no honorarium, grant, or other form of payment given to any of the authors/coauthors.

Compliance with ethical standards

Ethical approval Not applicable.

Conflict of interest No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

References

1. Papadopoulou M, Panagopoulou P, Papadopoulou A, Hatzipantelis E, Efstratiou I, Galli-Tsinopoulou A, et al. The multiple faces of Langerhans cell histiocytosis in childhood: a gentle reminder. Mol Clin Oncol. 2018;8:489–92.
2. Yurkovich M, Wong A, Lam JM. Solitary congenital self-healing Langerhans cell histiocytosis: a benign variant of Langerhans cell histiocytosis? Dermatol Online J. 2013;19:3.
3. Papo M, Cohen-Aubart F, Trefond L, Bauvois A, Amoura Z, Emile JF, et al. Systemic histiocytosis (Langerhans cell histiocytosis, Erdheim–Chester disease, Destombes–Rosai–Dorfman disease): from oncogenic mutations to inflammatory disorders. Curr Oncol Rep. 2019;21:62.
4. Langerhans P. Uber die nerven der menschlichen haut. Arch Pathol Anat. 1868;44:325–7.
5. Allen CE, Merad M, McClain KL. Langerhans-cell histiocytosis. N Engl J Med. 2018;379:856–68.
6. Khung S, Budzik JF, Amzallag-Bellenger E, Lambilliote A, Soto Ares G, Cotten A, et al. Skeletal involvement in Langerhans cell histiocytosis. Insights Imaging. 2013;4:569–79.
7. McClain KL. Clinical manifestations, pathologic features, and diagnosis of Langerhans cell histiocytosis. In: Post TW, editor. Up To Date. Waltham, MA.
8. Flores-Terry MA, Sanz-Trenado JL, García-Arpa M, Cortina-de la Calle MP. Cutaneous Langerhans cell histiocytosis presenting in adulthood. Actas Dermosifiliogr. 2019;110:167–9.
9. Jezierska M, Stefanowicz J, Romanowicz G, Kosiak W, Lange M. Langerhans cell histiocytosis in children—a disease with many faces. Recent advances in pathogenesis, diagnostic examinations and treatment. Postepy Dermatol Alergol. 2018;35:6–17.
10. Morren MA, Vanden Broecke K, Vangeebergen L, Sillevis-Smitt JH, Van Den Berghe P, Hauben E, et al. Diverse cutaneous presentations of Langerhans cell histiocytosis in children: a retrospective cohort study. Pediatr Blood Cancer. 2016;63:486–92.
11. Poompuen S, Chaiyarit J, Techasatian L. Diverse cutaneous manifestation of Langerhans cell histiocytosis: a 10-year retrospective cohort study. Eur J Pediatr. 2019;178:771–6.

12. Bi L, Sun B, Lu Z, Shi Z, Wang D, Zhu Z. Langerhans cell histiocytosis with multisystem involvement in an infant: a case report. Exp Ther Med. 2015;9:2137–40.
13. Merglová V, Hrušák D, Boudová L, Mukenšnabl P, Valentová E, Hostička L. Langerhans cell histiocytosis in childhood—review, symptoms in the oral cavity, differential diagnosis and report of two cases. J Craniomaxillofac Surg. 2014;42:93–100.
14. Yoon JH, Park HJ, Park SY, Park BK. Langerhans cell histiocytosis in non-twin siblings. Pediatr Int. 2013;55:e73–e7676.
15. McCullough WP, Pollock AN. Langerhans cell histiocytosis presenting as chronic otitis externa. Pediatr Emerg Care. 2017;33:67–9.
16. Iraji F, Poostiyan N, Dehnavi PR, Soghrati M. Langerhans cell histiocytosis: a case report with unusual cutaneous manifestation. Adv Biomed Res. 2018;7:102.
17. DiCaprio MR, Roberts TT. Diagnosis and management of Langerhans cell histiocytosis. J Am Acad Orthop Surg. 2014;22:643–52.
18. Peckham-Gregory EC, McClain KL, Allen CE, Scheurer ME, Lupo PJ. The role of parental and perinatal characteristics on Langerhans cell histiocytosis: characterizing increased risk among Hispanics. Ann Epidemiol. 2018;28:521–8.
19. Aboud MJ, Kadhim MM. Langerhans-cell histiocytosis (LCH) a presentation of two siblings with two different entities. Springerplus. 2015;4:351.
20. Aricò M, Nichols K, Whitlock JA, Arceci R, Haupt R, Mittler U, et al. Familial clustering of Langerhans cell histiocytosis. Br J Haematol. 1999;107:883–8.
21. Badalian-Very G, Vergilio JA, Degar BA, Rodriguez-Galindo C, Rollins BJ. Recent advances in the understanding of Langerhans cell histiocytosis. Br J Haematol. 2012;156:163–72.
22. Egeler RM, Favara BE, van Meurs M, Laman JD, Claassen E. Differential In situ cytokine profiles of Langerhans-like cells and T cells in Langerhans cell histiocytosis: abundant expression of cytokines relevant to disease and treatment. Blood. 1999;94:4195–201.
23. Crooks B, Grenier D. Langerhans cell histiocytosis: a complex recurrent disease. Paediatr Child Health. 2010;15:69–70.
24. Morimoto A, Oh Y, Shioda Y, Kudo K, Imamura T. Recent advances in Langerhans cell histiocytosis. Pediatr Int. 2014;56:451–61.
25. Tillotson CV, Patel BC. Langerhans cell histiocytosis. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019.
26. Monsereenusorn C, Rodriguez-Galindo C. Clinical characteristics and treatment of Langerhans cell histiocytosis. Hematol Oncol Clin N Am. 2015;29:853–73.
27. Nann D, Schneckenburger P, Steinhilber J, Metzler G, Beschorner R, Schwarze CP, et al. Pediatric Langerhans cell histiocytosis: the impact of mutational profile on clinical progression and late sequelae. Ann Hematol. 2019;98:1617–1626.
28. Ozer E, Sevinc A, Ince D, Yuzuguldu R, Olgun N. BRAF V600E mutation: a significant biomarker for prediction of disease relapse in pediatric Langerhans cell histiocytosis. Pediatr Dev Pathol. 2019;9:1093526619847859. https://doi.org/10.1177/1093526619847859.
29. Thacker NH, Abla O. Pediatric Langerhans cell histiocytosis: state of the science and future directions. Clin Adv Hematol Oncol. 2019;17:122–31.
30. Krooks J, Minkov M, Weatherall AG. Langerhans cell histiocytosis in children: History, classification, pathobiology, clinical manifestations, and prognosis. J Am Acad Dermatol. 2018;78:1035–44.
31. Weitzman S, Egeler RM. Langerhans cell histiocytosis: update for the pediatrician. Curr Opin Pediatr. 2008;20:23–9.
32. Bender NR, Seline AE, Siegel DH, Sokumbi O. Langerhans cell histiocytosis with prominent nail involvement. J Cutan Pathol. 2019;46:1–5.
33. Satter EK, High WA. Langerhans cell histiocytosis: a review of the current recommendations of the Histiocyte Society. Pediatr Dermatol. 2008;25:291–5.
34. Donadieu J, Chalard F, Jeziorski E. Medical management of Langerhans cell histiocytosis from diagnosis to treatment. Expert Opin Pharmacother. 2012;13:1309–22.
35. Haupt R, Minkov M, Astigarraga I, Schäfer E, Nanduri V, Jubran R, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Pediatr Blood Cancer. 2013;60:175–84.
36. Jeunon T, Sousa MA, Santos-Rodrigues N, Lopes R. Langerhans cell histiocytosis—a case report. Dermatol Pract Concept. 2012;2:25–9.
37. Windebank K, Nanduri V. Langerhans cell histiocytosis. Arch Dis Child. 2009;94:904–8.
38. Grifo AH. Langerhans cell histiocytosis in children. J Pediatr Oncol Nurs. 2009;26:41–7.
39. Hu S, Wang W, Wang C, Ma R, Xiao Z, Dong H. Langerhans cell histiocytosis presenting as a multi-system disorder in an infant. Int J Dermatol. 2012;51:709–12.
40. Mehta B, Amladi S. Langerhans cell histiocytosis presenting as hypopigmented papules. Pediatr Dermatol. 2010;27:215–7.
41. Chan MMH, Tan DJA, Koh MJ, Tan LS. Blistering Langerhans cell histiocytosis. Lancet Oncol. 2018;19:e500.
42. Fernández Armenteros JM, Arco Huguet N, Sanmartin Novell V, Vilardell Villellas F, Velasco Sanchez A, Martró Català E, et al. Langerhans cell histiocytosis mimicking molluscum contagiosum: a case series. Pediatr Blood Cancer. 2018;65:e27047.
43. Karpman MS, AlJasser MI, Lam JM. Molluscum contagiosum-like presentation of Langerhans cell histiocytosis: a case and review. Pediatr Dermatol. 2017;34:e288–e9.
44. Mori S, Adar T, Kazlouskaya V, Alexander JB, Heilman E, Glick SA. Cutaneous Langerhans cell histiocytosis presenting with hypopigmented lesions: report of two cases and review of literature. Pediatr Dermatol. 2018;35:502–6.
45. PDQ Pediatric Treatment Editorial Board. Langerhans cell histiocytosis treatment (PDQ®): Health professional version. PDQ cancer information summaries [Internet]. Bethesda: National Cancer Institute (US). 2002–2019.
46. Wollina U, Langner D, Hansel G, Schönlebe J. Cutaneous Langerhans cell histiocytosis: the spectrum of a rare cutaneous neoplasia. Wien Med Wochenschr. 2018;168:243–7.
47. Figueras-Nart I, Vicente A, Sánchez-Schmidt J, Jou-Muñoz C, Bordas-Orpinell X, Celis-Passini VP, et al. Langerhans cell histiocytosis presenting as fingernail changes. JAAD Case Rep. 2016;2:485–7.
48. Sabui TK, Purkait R. Nail changes in Langerhans cell histiocytosis. Indian Pediatr. 2009;46:728–9.
49. Aviner S, Ronen M, London D, Tobar A, Zangen S. Langerhans cell histiocytosis in a premature baby presenting with skin-isolated disease: case report and literature review. Acta Paediatr. 2008;97:1751–4.
50. Murata S, Yoshida Y, Adachi K, Morita E, Yamamoto O. Solitary, late-onset, self-healing Langerhans cell histiocytosis. Acta Derm Venereol. 2011;91:103–4.
51. Pettinger KJ, Solman L, Mathew B, Taylor G, Clark S, Picton S. Cutaneous Langerhans cell histiocytosis presenting in a neonate. Arch Dis Child. 2018;103:993.
52. Yu J, Rubin AI, Castelo-Soccio L, Perman MJ. Congenital self-healing Langerhans cell histiocytosis. J Pediatr. 2017;184:232–232.e1.
53. Kim JE, Kim BJ, Kang H. Solitary congenital erosion in a newborn: report of a solitary congenital self-healing reticulohistiocytosis. Ann Dermatol. 2014;26:250–3.
54. Mandel VD, Ferrari C, Cesinaro AM, Pellacani G, Del Forno C. Congenital, "self-healing" Langerhans cell histiocytosis

(Hashimoto–Pritzker disease): a report of two cases with the same cutaneous manifestations but different clinical course. J Dermatol. 2014;41:1098–101.
55. Parimi LR, You J, Hong L, Zhang F. Congenital self-healing reticulohistiocytosis with spontaneous regression. An Bras Dermatol. 2017;92:553–5.
56. Dabas A, Batra A, Khadgawat R, Jyotsna VP, Bakhshi S. Growth and endocrinal abnormalities in pediatric Langerhans cell histiocytosis. Indian J Pediatr. 2016;83:657–60.
57. Garofalo D, Cutfield R. Pituitary involvement in Langerhans-cell histiocytosis. N Z Med J. 2010;123:88–91.
58. Leung AK, McArthur RG. Histiocytosis X: sequential involvement of thirst and antidiuretic hormone centres. J R Soc Med. 1988;81:109–10.
59. Bravo MT, Garmendia M, Blanco SB, Etxezarraga C, Paja M. Langerhans cell histiocytosis: a rare cause of cholestasis in adult patients. Case report. Rev Esp Enferm Dig. 2010;102:571–2.
60. Leung AK, Chan KW. Iron deficiency anemia. Adv Pediatr. 2001;48:385–408.
61. McClain KL. Treatment of Langerhans cell histiocytosis. In: Post TW, editor. Up To Date. Waltham, MA. Accessed 22 June 2019.
62. Frade AP, Godinho MM, Batalha ABW, Bueno APS. Congenital Langerhans cell histiocytosis: a good prognosis disease? An Bras Dermatol. 2017;92:40–2.
63. Maglie R, Vannucchi M, Quintarelli L, Caproni M, Massi D, Antiga E. At the root: cutaneous Langerhans cell histiocytosis. Am J Med. 2018;131:922–6.
64. Park L, Schiltz C, Korman N. Langerhans cell histiocytosis. J Cutan Med Surg. 2012;1:45–9.
65. Yang YS, Byun YS, Kim JH, Kim HO, Park CW. Infantile scabies masquerading as Langerhans cell histiocytosis. Ann Dermatol. 2015;27:349–51.
66. Behera B, Malathi M, Prabhakaran N, Divya K, Thappa DM, Srinivas BH. Dermoscopy of Langerhans cell histiocytosis. J Am Acad Dermatol. 2017;76:S79–S81.
67. Ece D, Sahiner N, Ozkaya-Parlakay A, Oguz-Erdogan AS, Ozyoruk D, Tezer H, et al. Langerhans cell histiocytosis presenting like lichen planus in a 4-month-old infant. Pediatr Neonatol. 2018;59:219–20.
68. Lozano Masdemont B, Gómez-Recuero Muñoz L, Villanueva Álvarez-Santullano A, Parra Blanco V, Campos Domínguez M. Langerhans cell histiocytosis mimicking lichen nitidus with bone involvement. Australas J Dermatol. 2017;58:231–3.
69. Leung AK. The natural history of molluscum contagiosum in children. Lancet Infect Dis. 2015;15:136–7.
70. Leung AKC, Barankin B, Hon KLE. Molluscum contagiosum: an update. Recent Pat Inflamm Allergy Drug Discov. 2017;11:22–31.
71. Kalpana S, Lakshmi V. Systemic congenital Langerhans cell histiocytosis masquerading as diffuse neonatal hemangiomatosis. Indian Pediatr. 2018;55:613.
72. Leung AK, Rafaat M. Benign neonatal hemangiomatosis. Pediatr Dermatol. 2003;20:161–3.
73. Rubio-González B, García-Bracamonte B, Ortiz-Romero PL, Postigo-Llorente C, Vanaclocha-Sebastián F. Multisystemic Langerhans cell histiocytosis mimicking diffuse neonatal hemangiomatosis. Pediatr Dermatol. 2014;31:e87–9.
74. Leung AKC, Lam JM, Leong KF. Childhood solitary cutaneous mastocytoma: clinical manifestations, diagnosis, evaluation, and management. Curr Pediatr Rev. 2019;15:42–6.
75. Billings TL, Barr R, Dyson S. Langerhans cell histiocytosis mimicking malignant melanoma: a diagnostic pitfall. Am J Dermatopathol. 2008;30:497–9.
76. Punja M, McWey RP, Heller M. Lytic lesion. J Emerg Med. 2013;44:179–80.
77. Leung AKC, Robson WLM, Halperin ML. Polyuria in childhood. Clin Pediatr. 1991;30:634–40.
78. Leung AK, Rafaat M. Eruption associated with amoxicillin in a patient with infectious mononucleosis. Int J Dermatol. 2003;42:553–5.
79. Leung AKC, Leong KF, Lam JM. A case of congenital syphilis presenting with unusual skin eruptions. Case Rep Pediatr. 2018;2018:1761454.
80. Ramachandran R. Case 3: hepatosplenomegaly in a 2-year-old boy. Pediatr Rev. 2015;36:265–7.
81. Berliner N. Approach to the adult with unexplained pancytopenia. In: Post TW, editor. UpToDate. Waltham, MA. Accessed 12 June 2019.
82. Sharma R, Nalepa G. Evaluation and management of chronic pancytopenia. Pediatr Rev. 2016;37:101–11 **(quiz 112-3)**.
83. Leung AK, Hon KL, Leong KF, Sergi CM. Measles: a disease often forgotten but not gone. Hong Kong Med J. 2018;24:512–20.
84. Leung AKC, Hon KL, Leong KF. Rubella (German measles) revisited. Hong Kong Med J. 2019;25:134–41.
85. Leung AK, Robson WL. Childhood cervical lymphadenopathy. J Pediatr Health Care. 2004;18:3–7.
86. Leung AK, Davies HD. Cervical lymphadenitis: etiology, diagnosis, and management. Curr Infect Dis Rep. 2009;11:183–9.
87. Herman TE, Siegel MJ. Langerhans cell histiocytosis: radiographic images in pediatrics. Clin Pediatr (Phila). 2009;48:228–31.
88. Madasu A, Noor Rana A, Banat S, Humad H, Mustafa R, AlJassmi AM. Langerhans cell histiocytosis in an infant mimicking a lymphoma at presentation. Case Rep Hematol. 2015;2015:670843.
89. Leung AKC, Leong KF, Lam JM. Onychomadesis in a 20-month-old child with Kawasaki disease. Case Rep Pediatr. 2019;2019:3156736.
90. Aricò M. Langerhans cell histiocytosis in children: from the bench to bedside for an updated therapy. Br J Haematol. 2016;173:663–70.
91. Leung AKC, Leung AAC. Evaluation and management of the child with hypothyroidism. World J Pediatr. 2019;15:124–34.
92. Ma J, Laird JH, Chau KW, Chelius MR, Lok BH, Yahalom J. Langerhans cell histiocytosis in adults is associated with a high prevalence of hematologic and solid malignancies. Cancer Med. 2019;8:58–66.
93. Park IS, Park IK, Kim EK, Kim S, Jeon SR, Huh JR, et al. Langerhans cell histiocytosis followed by Hodgkin's lymphoma. Korean J Intern Med. 2012;27:459–62.
94. Minkov M. An update on the treatment of pediatric-onset Langerhans cell histiocytosis through pharmacotherapy. Expert Opin Pharmacother. 2018;19:233–42.
95. Chow TW, Leung WK, Cheng FWT, Kumta SM, Chu WCW, Lee V, et al. Late outcomes in children with Langerhans cell histiocytosis. Arch Dis Child. 2017;102:830–5.
96. Kaiserian M, Altberg G, Greenstein J, Hahn B. Langerhans cell histiocytosis. J Emerg Med. 2019;56:e31–2.