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Langerhans cell histiocytosis: Diagnosis and Management

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Abstract

Langerhans cell histiocytosis (LCH) is a rare disorder characterized by abnormal clonal proliferation of Langerhans dendritic cells. The incidence of LCH is 1 to 3 cases per 1 million children worldwide, and occurs most frequently in children of 1–4 years of age. The etiopathogenesis of LCH, whether it is neoplastic or reactive, is still controversial. Langerhans cell histiocytosis has a wide spectrum of clinical features, and dermatological abnormalities usually occur early. The most frequent lesions are elevated yellowish-red translucent papules about 1–2 mm in diameter and generally located in seborrheic areas. The most recent classification (the Histiocyte Society study 2017) categorized LCH into four groups; a single system with involvement of unifocal or multifocal organs, lung LCH, and multi-system LCH with either low- or high-risk multiorgan involvement. The definitive diagnosis of LCH are typical morphology along with Birbeck granules and/or positive results on CD1a antigen stain on cells found on lesions. Treatment of LCH is multimodal, determined based on age, extent of lesion, organ involvement, and organ location.

Keywords: *histiocytosis, Langerhans cells, dendritic cells, children*

Introduction

Histiocytosis is a group of diseases marked by the proliferation, infiltration, and accumulation of cells that are part of mononuclear phagocyte system, especially dendritic cells, in several tissues or body organs.¹ Langerhans cell histiocytosis (LCH) is a rare disorder based on the abnormal clonal growth of Langerhans dendritic cells.¹⁻²

The etiopathogenesis of LCH is still unclear, but it is suggested to be either a reactive or neoplastic abnormality.^{1,2} Clinical symptoms of LCH vary with skin involvement being the initial complaint.² The most recent classification categorized LCH into a single system with the involvement of unifocal or multifocal organs, lung LCH, and multi-system LCH with either low- or high-risk multiorgan involvement.³

The prevalence of LCH in the world ranges from 4 to 5.4 cases per 1 million population. The annual incidence is estimated to be 0.5 per 100,000 children in the United States and 2–9 cases per 1 million children in the world.¹ Epidemiologic studies in children in France have identified 1478 patients with LCH in 30 years since 1983.⁴ This disease can occur at any age, even congenitally. The case occurs most frequently in children of 1–4 years old⁵ with a male-to-female ratio of 2:1.^{1,2} In Indonesia, the incidence of LCH is low; 17 new LCH cases had been detected in the Pediatric and Dermatovenereology Department of Hasan Sadikin General Hospital in 2012–2015.⁶ In the Pediatrics Division of Faculty of Medicine Universitas Indonesia Dr. Cipto Mangunkusumo National Central General Hospital, 64 cases had been reported since 2005–2016; in 2013–2016, 10 new pediatric cases of LCH were detected in the Dermatovenereology Clinic of the Pediatrics

Division of Dr. Cipto Mangunkusumo National Central General Hospital.

Etiopathogenesis

Histiocytosis is caused by deviation in the proliferation or activation of dendritic cells or macrophages in the mononuclear phagocyte system.^{2,3} LCH is marked by inflammatory lesions containing many histiocytes expressing CD1a+ and CD207+.⁸

The pathogenesis of LCH is still unclear. Several studies suggest that the etiology of LCH is multifactorial, including genetic factors, infections due to viruses or tuberculosis, cellular and immune system dysfunction, cellular adhesive molecules, or a combination of several factors.^{2,3,12}

Two hypotheses are still under investigation. The first hypothesis states that LCH is a reactive disease based on the following: (1) LCH cells are highly differentiated, (2) histological examinations show granulomatous lesions similar to tissue reaction during infection (especially viral infection) or foreign bodies, and (3) lesions can regress spontaneously. The pathogenesis in this hypothesis is (1) the virus/foreign body induces the activation of histiocytes, (2) the immunological mechanism produces pathological Langerhans cell phenotype, (3) the antigenic stimulation causes exaggerated host immune response, a phenomenon known as cytokine storm.^{2,10}

The second hypothesis states that LCH is a neoplastic disorder that is based on (1) LCH cell clonal growth in the bone marrow, (2) familial LCH cases, (3) unstable chromosome has been found, with abnormalities in chromosome 7 and protein p53, and (4) concurrent LCH and myelodysplasia.²⁻¹⁰ In addition, BRAFV-600E mutations have been found through DNA sequencing. Mutations appear in about 50% of LCH lesions, and this pathway is activated in all lesions. Hyperactivity of the MAPK pathway, such as MAP2K1 or ARAF, is also found in 10%–25% of cases.⁹ These findings support the possibility of effective chemotherapy toward immature myeloid cells and a specific target therapy aimed at specific mutations.²

Clinical Finding

Classification

Patients with LCH exhibit a variety of symptoms and clinical findings. In the previous classification, LCH was divided into several variants. The **first variant**, *Abt–Letterer–Siwe* disease, also known as

disseminated LCH with hematological dysfunction, is acute and frequently occurs in neonates. Skin lesions resembling seborrheic dermatitis that may appear in the palms, soles, and nails are usually the first manifestation. The natural history of the disease may subsequently involve multiple organs.¹¹ The **second variant**, *Hand–Schuller–Christian* (HSC) disease, is a multi-systemic, chronic, and progressive disease that usually begins at the age of 2–6 years. The triad of symptoms includes diabetes insipidus, bone (osteolytic) lesions, and exophthalmos. The **third variant**, eosinophilic granuloma, is a form of localized LCH and is found more frequently than the other variants; it is prevalent in older children or even adults and is more dominant in males than in females. The lesion is most frequently manifested as granulomatous lesion in bones; lesions in the skin and mucous layer are rarely found. Hashimoto–Pritzker disease or *congenital self-healing reticulohistiocytosis* is a variant of LCH that is limited to the skin without systemic involvement and is self-limiting. The lesions commonly emerge since birth or a few days after birth in the form of red-brown papules or nodes that become crusted ulcerations in a couple of weeks; the lesion may involute at the age of 2–3 months.¹¹ Despite its self-limiting nature, this variant may recur with complications; thus, follow-up is still advised for the following years.¹³

Since 1987, the Histiocyte Society has made several revisions to the disease classification. The latest classification is based on the number of body areas presenting with the lesions and the involvement of high-risk organs, including the hematopoietic system, liver, or spleen.^{2,9,14} The purpose of this new classification is for clinical interests and for determining the therapy and prognosis.^{2,11} The LCH-III study divides LCH into two categories in accordance with the type, number, and extent of tissues involved.^{2,10,15} Sixty five percent of patients with LCH have a single-system disease with very good prognosis. Dermatological involvement is found in 12% of pediatric patients with single system (S-S) LCH and 53% of multi-system (M-S) LCH.¹⁰ Lung organ involvement, which was included in the previous classification as the high-risk MS group, apparently does not have a very crucial prognostic role based on LCH-III results.¹⁵

In 2017, the Histiocyte Society study group provided a new classification. Histiocytosis is classified into five primary groups (groups L, C, M, R, and H) in accordance with clinical, radiologic, pathologic, phenotypic, genetic, and molecular factors. Langerhans cell histiocytosis is included in

the L group and is classified into 4 groups; single system (S-S) LCH, lung LCH, multi-system (M-S) LCH (low risk) and multi-system (M-S) LCH (high risk; hematopoietic system, liver and spleen).¹⁶

Skin Lesions

Skin lesions in LCH vary, including eczematous lesions, macules, papules, vesicles, nodes, erosions, and ulcerations. The most frequent lesions are elevated yellowish-red translucent papules that are 1–2 mm in diameter and generally located in the trunk, scalp, and behind the ears.^{2,3,10} Oily, squamous lesions in skin folds mimicking seborrheic dermatitis are also frequently observed, which are sometimes accompanied with crusts and ulcerations.¹⁰ Vesicles and pustules may resemble eczema, miliaria, scabies, and varicella. These morphologies are frequently discovered in neonates.² The presence of purpura denotes a poor prognosis.² A report has been published on a neonate with red-blue nodes known as the “blueberry muffin baby”.¹⁰

Skin lesions may appear and grow rapidly (Figure 1). Lesions in the scalp tend to merge, resembling seborrheic dermatitis or folliculitis and may result in alopecia. Lesions in skin folds may mimic intertrigo. Sometimes, lesions merge to form plaques in the medial chest, middle part of the back, temporoparietal, and may become xanthomatous.²

Changes in the nail (Figure 2) include easily-cracked lamina, paronychia, subungual pustules, destruction of nailfolds, onycholysis, subungual hyperkeratosis, longitudinal grooves, purpuric

linear lesions, or pigmentations on the nails. Nail involvement is rare, but its involvement indicates poorer prognosis.^{1,2,11} Mucous lesions and external otitis are generally discovered in M-S LCH.¹⁰ Mucous membrane lesions are generally nodulo-ulcerative lesions. Oral manifestations may be the first sign of LCH, appearing as non-specific pain, aphthous stomatitis, ulceration, and recurrent bleeding in the gingivae, so that the patient appears to have “floating teeth”.⁴

Other Symptoms

Weight loss, nausea, malaise, growth failure, myalgia and arthralgia, and fever are frequently found. Bone lesions appear in 80% of cases, most of which are in the skull, femur, mandibula, pelvis, and vertebra.² Bone marrow involvement is rare and usually appears in the late stage marked by a high number of histiocytes. A poor prognosis is marked by thrombocytopenia, leukopenia, and anemia.^{2,11} Lung involvement may be asymptomatic but may also cause death especially in geriatric patients. Hepatosplenomegaly caused by Langerhans cell infiltration or hyperplasia of Kupffer cells is often accompanied with complications and is also generally a marker of poor prognosis.

Involvement of mucosal lining of the digestive tract and lymph nodes is rare and may be found in fatal cases. Diabetes insipidus and exophthalmos occur in 50% and 10%–30% of cases, respectively, whereas involvement of the central nervous system is rarely found.²



Figure 1. Skin Lesion in Langerhan Cell Histiocytosis



Figure 2. Nail Manifestation in Langerhan Cell Histiocytosis

Diagnostic Workup

Laboratory Evaluation

Complete blood count, blood chemistry, and coagulation factors are performed to evaluate general condition.² Complete peripheral blood examination is needed to evaluate cytopenia, whereas liver function tests are important to evaluate liver involvement marked by elevated transaminases, hyperbilirubinemia, and hypoalbuminemia.⁴

Imaging Studies

Imaging studies includes skeletal survey or positron emission tomography scan to evaluate bone involvement. Computed tomography of the head and chin is performed to detect bone lesions, whereas magnetic resonance imaging (MRI) is performed to evaluate the central nervous system. Other examination such as chest X-ray is performed to evaluate respiratory organ involvement and abdominal ultrasound is used to evaluate digestive organ involvement.²

Histologic Findings

Dense infiltration of lymphomonocytic cells in dermal areas with kidney-shaped nuclei may be a sign of LCH (Figure 3). A definite diagnosis is established by detection of the expression of CD1a, S100, and CD 207 (langerin) in immunohistochemical histopathologic examination. Langerin is a type 2 transmembrane C-type lectin associated with the formation of Birbeck granules in Langerhans cells and is a specific marker for LCH.¹⁸ Electron microscopy may be performed to find Birbeck granules.⁵

Skin biopsy or cell cytology are mandatory for diagnosis.² There are also several other

examinations to evaluate organ involvement such as endoscopy and biopsy to evaluate malabsorption, bone marrow biopsy to evaluate the cause of pancytopenia, lung function to evaluate tachypnea and evaluation before chemotherapy, bronchoalveolar lavage to search infiltration of respiratory tract, lung biopsy to rule out opportunistic infection, and endocrine evaluation (growth hormone level evaluation in case of short stature and hypothalamic syndrome; TSH level in case of galactorrhea and precocious puberty).²

Diagnosis

The Histiocyte Society established a guideline on the diagnosis and therapeutic options for patients suspected with LCH. The skin lesion criteria are (1) **presumptive diagnosis:** based on the characteristics of lesion morphology; (2) **designated diagnosis:** typical morphology along with two or more positive results from adenosine triphosphate, protein S100, α -D-mannosidase, and peanut lectin stains; and (3) **definitive diagnosis:** typical morphology along with Birbeck granules found on lesions and/or positive results on CD1a antigen stain on cells found on lesions.²

Differential Diagnosis

LCH skin lesions have a variety of presentations and thus may mimic other skin disorders. the differential diagnoses are based on the type of lesions (papular, vesico-papular, xanthomatous, and nodulo-ulcerative) and location of lesion (scalp, face, intertriginous areas and trunk) which divided into two categories as highly likely and considered.²

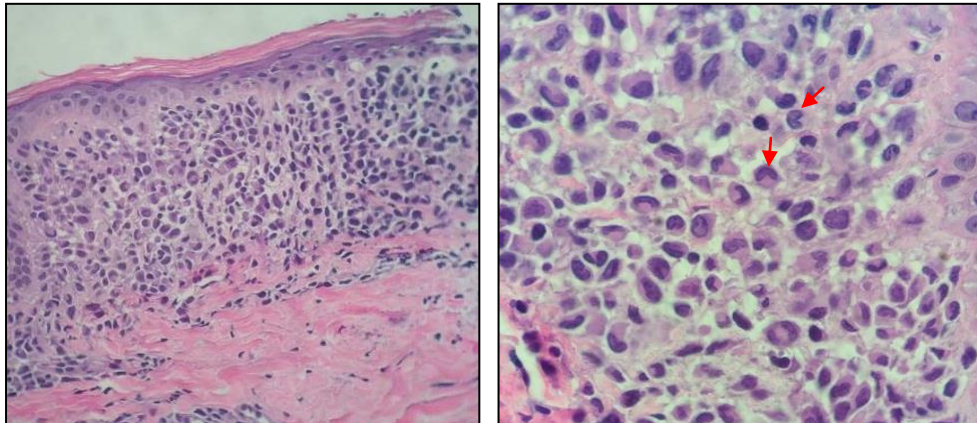


Figure 3. Infiltration of Lymphomonocytic Cells in Dermal Areas with Kidney-shaped Nuclei (red arrow)

Management

Management strategy for LCH depends on multiple factors, including patient's age, location of lesion, and number of organs involved. The management is multimodal, beginning from periodic observation to topical therapy, chemotherapy, surgery, radiotherapy, phototherapy, or a combination of these modalities.¹⁹ Systemic therapy in low-risk MS-LCH is needed to control the severity of disease and to prevent reactivation and permanent complications. Patients with high-risk organ involvement may not respond to therapy, which results in disease reactivation with permanent complications.¹⁵

There's still no standardized therapy protocol for LCH skin lesions.¹⁰ In S-S LCH, routine and periodic observation of the skin lesions are the only management needed. Topical corticosteroids may be the first-line therapy for eczematous lesions. In nodulo-ulcerative or papulonecrotic lesions, Morren et al.¹⁰ recommends observing the lesion until they spontaneously disappear, with the application of topical antiseptic or antibiotic as necessary. Other studies have reported successful therapies using intralesion corticosteroids for plaque and nodular lesions.²⁰⁻²¹ In severe and limited/minimal skin lesions, the choice includes alkylating antineoplastic agents such as topical nitrogen mustard or carmustin. Topical tacrolimus and imiquimod may also be used.² For periorificial granulomatous lesions, CO₂ laser may be used.²

LCH with extensive skin involvement sometimes needs systemic therapy. In some cases, oral thalidomid and isotretinoin are successful.² A combination of systemic corticosteroids and

antibiotics is recommended in cases of resistant skin lesion.² Steen et al.²² reported successful therapy using intravenous 20 mg methotrexate weekly in an adult patients with skin LCH resistant to PUVA therapy. Kwon et al.²³ showed that psoralen and ultraviolet A (PUVA) are effective in cases resistant to oral systemic therapy. PUVA is only advised for older children and administered shortly because of its phototoxicity and risk of secondary malignancy.²³⁻²⁴

Narrow-band ultraviolet B may be a safer choice for radiation therapy and is reported to be successful for LCH skin lesion in children.²⁴ In a case report of adult LCH with multiple erythematous lesions without therapy for 20 years, narrow-band ultraviolet B radiation was given 1–2 times weekly with an increase in dosage by 20% per visit, and improvement was observed in the 4th radiation.²⁰ In another study on a 15-month old patient with LCH skin lesion, radiation was performed with local phototherapy, starting with a dose of 200 mJ/cm² with a duration of 1 minute and 15 seconds, to a maximum of 6 minutes per area. After 3 months, the skin lesion was reported to be in total remission.²⁵

The Histiocyte Society has conducted three major studies, LCH-I, LCH-II, and LCH-III, to seek therapy for M-S LCH. The LCH-I study (April 1st 1991-October 1st 1995) compared etoposide (VP-16) and vinblastine for therapy of LCH M-S.²⁶ The result showed that vinblastine and etoposide, along with corticosteroids, are equally effective for LCH M-S.²⁷ In LCH-II (May 1st 1996-March 31st 2001), patients with M-S LCH are divided into two groups. The first group received prednisone daily and vinblastin weekly for 6 weeks, continued with 6-mercaptopurine for 18 weeks. For the second

group, etoposide was added. This study concluded that intensive therapy with the addition of etoposide in the combination therapy of prednisolone and vinblastine increases response to therapy and decreases patient mortality in M-S LCH.²⁸

LCH-III (April 1st 2001-February 10th 2008) was conducted based on the high reactivation rate in M-S LCH to test the efficacy of increasing the duration of therapy. LCH-III did not include etoposide in the protocol and substituted it with methotrexate. The result showed that 12-month therapy suppressed the number of reactivation.²⁹

Another report showed the efficacy of cyclosporin A, TNF- α inhibitor, biphosphonate, indomethacin, 2-chlorodeoxyadenosine, and interferon- α to allogeneic bone marrow transplantation or umbilical blood transplantation for LCH therapy. Chemotherapy is usually performed by a pediatrician from the hematooncology division. Chemotherapy may be intensive immediately after diagnosis or conservatively, which entails chemotherapy only during exacerbation.³⁰

The therapy protocol in the Pediatrics Department of Dr. Cipto Mangunkusumo National Central General Hospital at present is based on the study by Gadner et al.²⁸ which is a modification of the study result of LCH-II. Initial therapy for 6 weeks using intravenous bolus of 6 mg/m² of vinblastine and intravenous drip of 150 mg/m² of etoposide for 1 hour was given once weekly, along with oral prednisone 40 mg/m² daily, with full dosage given for 4 weeks and the dosage was reduced for the last 2 weeks. The therapy is followed with the same regiment given every 3 weeks added with 50 mg/m² 6-mercaptopurine orally every day starting on the seventh week to a total of 24 weeks.

LCH-4 and Options of Therapy for the Future

The ongoing LCH-4 study aimed to answer several problems in therapeutic aspect, especially to reduce the mortality rate by 20% in high-risk MS-LCH, and to evaluate whether the increase in the duration of therapy can reduce the number of reactivations. To reduce mortality, two stratification steps are performed to identify patients with poorer prognostic probability, which includes the risk of organ involvement at initial diagnosis and response to standard initial therapy. Targeted therapy study using BRAF or MEK inhibitors, especially in refractory cases, may present a new opportunity for the management of LCH in the future.⁹

Complications

Secondary infection, especially candidosis and dermatophytosis, is frequently encountered in LCH skin lesions. Severe pyogenic abscess has been reported in geriatric patients. LCH may manifest in or complicate the gastrointestinal system and carry a poor prognosis.³¹ Other studies have shown the possibility of thymus and ophthalmologic involvement and complications. Sclerosing cholangitis may occur in 10%–15% of patients with visceral involvement of LCH.³²⁻³⁴ Sclerosing cholangitis may occur in a median of 2 years after diagnosis in children, although sometimes it may occur in adulthood during the remission phase of LCH. A diagnosis of sclerosing cholangitis is made using radiology examination and liver biopsy.³⁵ In a study conducted on a subject population of 589 LCH patients with a pediatric onset, 145 patients were found to have a complication of hypophysis dysfunction and 141 patients with diabetes insipidus.³⁶

Prognosis

The prognosis of patients with LCH varies and depends on multiple factors, including the extent of organ involvement, age, type and number of locations of lesion, organ dysfunction, and response to therapy. A univariate analytical study reported that the age below 1 year old; the involvement of ear, nose, throat, skin, lymph node, liver, spleen, lung, bone marrow, or digestive tract; male gender; progressive episode; and unresponsive or partially responsive to therapy are associated with poor prognosis.³⁷ A study conducted by Minkov¹⁵ reported a high risk of mortality in LCH patients with the involvement of the hematopoietic system, liver, and spleen, as well as those with poor response on the initial phase of therapy.

Dermatological LCH with or without other organ involvement at the time of diagnosis affects the prognosis.³⁸ The LCH-III study discovered that 5-year life expectancy in children with MS-LCH without high-risk organ involvement reaches 100%, but those with the involvement of high-risk organs have increased mortality rate to about 15%.¹⁰ The recurrence rate of S-S monoostotic LCH is estimated to be around 10%–25% in polyostotic LCH. In M-S LCH, around 50%–70% of cases recur after initial remission.^{4,6} After recovery, patients are advised to come for routine follow-up every 6 months for a minimum of 5 years.¹⁰

Conclusion

LCH is a disorder marked by the infiltration of histiocytes in several body organs and manifesting in various clinical symptoms. Skin involvement frequently occurs and is usually the first symptom, with the morphology mimicking other skin disorders. The recognition of this diagnosis is important to prevent delayed therapy. Management aims to achieve long-term recovery with a low rate of recurrence and to prevent neural degeneration. The LCH-IV study is still ongoing to seek the best therapeutic option. Targeted therapy with BRAF or MEK inhibitor may open a new opportunity for the management of LCH in the future.⁹

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