LEUKEMIA & LYMPHOMA SOCIETY®

Langerhans Cell Histiocytosis

No. 39 in a series providing the latest information for patients, caregivers and healthcare professionals

Highlights

- Langerhans cell histiocytosis (LCH) is a rare cancer that forms when the body makes too many immature Langerhans cells. Normal Langerhans cells, also called "histiocytes," help protect the body from infection. But in LCH, immature Langerhans cells multiply abnormally and grow in various parts of the body.
- Histiocytosis is the term for a group of rare disorders in which too many immature histiocytes build up in certain tissues and organs, including the skin, bones, spleen, liver, lungs and lymph nodes. They can damage tissue or form an abnormal mass (called a lesion or tumor).
- LCH has been classified in a variety of ways. The current proposed system for adult LCH describes four subtypes: 1. unifocal (single lesion), 2. single-system pulmonary (lung), 3. single-system multi-focal (two or more lesions in the same organ system) and 4. multi-system (two or more organs involved).
- Pulmonary (lung) LCH most commonly occurs by itself, but it may be part of a multi-system disease.
- LCH is most common in young children, but it can occur at any age.
- The *BRAF* V600E gene mutation is present in the histiocytic cells of more than half of LCH cases.
- There is wide variation in presentation, treatment and prognosis of LCH.

Introduction

Langerhans cell histiocytosis (LCH) is a rare cancer in which the body produces an excessive number of immature cells called Langerhans cells. Normal Langerhans cells are immune cells called histiocytes, which help the immune system destroy foreign materials and fight infection. But immature Langerhans cells can grow and build up in parts of the body where they can damage skin and organs or form lesions (abnormal tissues).

A "lesion" is an area of abnormal tissue that is damaged due to injury or disease. A "tumor" is an abnormal mass of tissue that forms when cells grow and divide more than they should, or do not die when they should. Lesions and tumors can be "benign" or "malignant." A benign lesion is not cancerous; it may grow but not spread. A malignant lesion is cancerous, which means it can invade nearby tissue or spread to other parts of the body. All tumors are lesions, but not all lesions are tumors.

LCH most commonly affects the skin and bones, but it can involve any organ in the body.

LCH is typically classified based on the site of the lesions and the number of involved lesions. LCH may be a "single-system" disease or "multi-system" disease. Single-system LCH most often involves the skin, bone, or lungs, the pituitary gland, the central nervous system (brain and spinal cord) or the lymph nodes. Single-system disease can be present in one site or many sites. Multi-system LCH involves 2 or more organ systems including the pituitary gland, liver, spleen, bone marrow, lungs, central nervous system and lymph nodes. A specific form of LCH affecting the lungs called "Pulmonary LCH" is associated with smoking. See **Table 1** below.

Table 1. Classification of LCH

Subtype	Definition
Unifocal	Solitary lesion involving any organ
Single-system pulmonary	Isolated lung involvement (usually smoking-related)
Single-system multi-focal	More than 1 lesion involving any organ
Multi-system	More than 2 organs or organ systems involved

Some classifications indicate whether a "risk organ" or "critical organ" is involved. Risk and critical organs are the bone marrow, the liver, the spleen, and the central nervous system. Involvement of these organs tends to indicate more serious disease. See **Table 2** on page 2 for additional categories of LCH.

Table 2. Additional Categories of LCH

Category	Description
Pulmonary LCH (PLCH)	Affects the lungs
Central nervous system (CNS LCH)	Involves the brain and spinal cord
Mixed histiocytosis	LCH occurs along with Erdheim-Chester disease or Rosai-Dorfman disease (See *Health Terms* on pages 9 and 10)
LCH associated with another cancer	LCH with a blood cancer (eg, leukemia or lymphoma) or a solid-tumor cancer (eg, lung or thyroid cancer)

Management of LCH varies. In some cases, LCH may be mild and can be monitored with observation. Other cases can be successfully treated with localized therapy (such as surgery or radiation). However, there are some cases that require systemic therapy (such as chemotherapy) if the disease is widespread or can progress rapidly, becoming life-threatening. When the disease occurs only in the skin, it may go away on its own. In single-system PLCH, the first line of treatment is always smoking cessation (to stop smoking completely).

LCH is thought to be caused by mutations in the *BRAF, MAP2K1, KRAS, NRAS* and *ARAF* genes of the histiocytic cells. The *BRAF* V600E gene mutation is present in the cells of more than half of LCH cases. Activation of the MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) pathway in the cells is found in most cases. These changes affect cell growth, development, division and death. Knowing this information can help doctors determine the best treatment for you.

Signs and/or Symptoms

A "sign" is a change in the body that the doctor sees in an examination or a test result. A "symptom" is a change in the body that a patient can see and/or feel.

The signs and symptoms of LCH vary depending on the location of the disease and extent of involvement of the internal organs. LCH most commonly affects the bones (especially the skull) and the skin, but any organ can be involved. LCH may be suspected with one or more of the symptoms listed below:

- **Bone**—bone lesions, bone pain, fractures
- **Skin**—skin lesions, skin rashes or flaking, nail changes
- **Lungs**—cough, shortness of breath, chest pain
- **Brain and Spinal Cord**—impaired balance or coordination, impaired speech, dizziness, difficulty walking, headache, seizures, altered mental status, behavior changes, memory difficulties
- **Eyes**—vision problems
- **Ears**—ear pain or redness, discharge from ear canal, hearing impairment
- **Mouth**—swollen or bleeding gums, mouth sores, loose teeth
- **Stomach**—abdominal or pelvic pain, diarrhea, vomiting, nausea, blood in stool, weight loss
- **Glands and Hormones**—increased thirst, frequent urination (See "diabetes insipidus" in *Health Terms* on page 9), growth delay, weight gain, fever, night sweats, decreased libido (sex drive)
- **Lymph Nodes**—enlarged lymph nodes (such as in the neck, groin, armpits)
- **Liver and Spleen**—enlarged liver or spleen (swelling of the abdomen), yellowing of the skin and whites of the eyes
- **Psychiatric**—depression or anxiety
- **Bone Marrow**—low numbers of red blood cells (fatigue or lack of energy), white blood cells (frequent infections), or platelets (easy bruising or bleeding)

Diagnosis

Diagnosis of LCH is based on the results of a thorough medical history, a comprehensive physical examination, tissue biopsy, laboratory studies and imaging tests. In some patients, neurocognitive (ability to think and reason) and psychological (mental and emotional health) assessments may be recommended.

Tissue Biopsy. A test often used to make a definitive diagnosis is a tissue biopsy. Biopsy of the skin, bone or soft tissue involves the removal of cells or tissues for examination by a pathologist (a doctor who specializes in the microscopic study of cells and tissues). The pathologist will see if the cells in the tissue sample meet the criteria for a diagnosis of LCH. The biopsy will also be used for genetic testing (such as next-generation sequencing) to check for the mutation in the *BRAF* V600E gene or other genes in the MAPK-ERK pathway. If single-system pulmonary LCH is suspected but a lung biopsy would not be safe, imaging tests (such as a high-resolution CT scan of the chest) may be used to help confirm the diagnosis.

Bone Marrow Aspiration and Biopsy. In some cases, a bone marrow aspiration and biopsy may be recommended. This is a procedure to remove and examine bone marrow cells to see if they are normal. A liquid sample of cells and a very small amount of bone filled with bone marrow cells is taken from the body. Then the cells are examined under a microscope.

Common lab tests that are used for LCH are found in **Table 3**, below.

Table 3. Lab Tests

Test	Purpose
C-reactive protein	A test used to measure the amount of C-reactive protein (CRP) in your blood. CRP levels can indicate the presence and severity of inflammation in the body.
Complete blood count (CBC) with differential	A comprehensive blood test used to measure and analyze the cells in your blood (red blood cells, white blood cells and platelets) and their characteristics. A "differential" measures the various types of white blood cells (neutrophils, lymphocytes, monocytes, eosinophils and basophils) in the sample.
Comprehensive metabolic panel	A blood test with 14 different measurements. It can detect a range of abnormalities in blood sugar and nutrient balance, and also evaluate liver and kidney health.
Erythrocyte sedimentation rate (ESR)	A test to measure how quickly red blood cells fall to the bottom of a test tube; its purpose is to check for inflammation.
FSH (follicle-stimulating hormone) and LH (luteinizing hormone) with testosterone (males) and estradiol (females)	Blood tests used to evaluate functioning of the pituitary gland as well as the health of the reproductive organs
Fusion assay	A test to detect gene fusions (the joining of two genes) in tissue samples
IGF-1 (insulin-like growth factor-1)	A test used to measure the amount of IGF-1 in the blood and to evaluate pituitary function. Along with growth hormone, IGF-1 helps promote normal bone and tissue growth and development.
Immunoglobulin profile	A test to check for an excess or deficiency of immunoglobulins (proteins in the immune system)
Lactate dehydrogenase	A test to measure the amount of tissue damage
Morning urine osmolality	A test of urine first thing in the morning to check its appearance, concentration and content. Decreased concentration of urine is associated with diabetes insipidus.
Morning serum cortisol with ACTH (adrenocorticotropic hormone)	A test taken first thing in the morning and used to determine if the adrenal glands are producing an appropriate amount of the hormone called "cortisol" in the blood, urine or saliva. Cortisol testing can help diagnose or rule out certain conditions.
Next-generation sequencing (NGS)	A technology used for determining the sequence of DNA (deoxyribonucleic acid) or RNA (ribonucleic acid) to study genetic variations associated with disease including the *BRAF* V600E mutation and MAPK-ERK pathway mutations like *MAP2K1, KRAS,* etc. This test is usually conducted on a tissue sample from the lesion biopsy but can be done using a blood sample if tissue is unavailable.
Polymerase chain reaction (PCR)	A very sensitive test used to determine the presence of certain genetic abnormalities, such as the *BRAF* V600E mutation, in blood or bone marrow cells.
Prolactin	A blood test used to measure the amount of prolactin in the body. Prolactin is a hormone produced by the pituitary gland.
Serum osmolality	A test used to measure the concentration of dissolved particles in the blood or urine that may signal fluid or electrolyte imbalance, including dehydration or diabetes insipidus. (Note: diabetes insipidus is different from diabetes mellitus, which is common and requires insulin injections. See diabetes insipidus in *Health Terms* on page 9.)
TSH (thyroid-stimulating hormone) and free T4 (thyroxine)	Blood tests used to see if the thyroid gland is functioning properly
Water deprivation test	A test to measure how much urine is made and how concentrated it becomes when no water is given to the patient for a certain amount of time, to see how well the kidneys work

Imaging tests (which provide "pictures" of the inside of the body), and other tests and procedures are also used to diagnose and monitor LCH. See **Table 4** on page 4. Your healthcare team will determine which tests and procedures to recommend, based on your symptoms or organ involvement.

Table 4. Imaging Tests and Procedures

Test or Procedure	Purpose
Bone scan	A procedure used to check for abnormal areas or damage in the bones. A very small amount of radioactive material is injected into a vein and travels through the blood. This radioactive material collects in the bones and then is detected by a scanner.
CT (computed tomography) scan of the chest, abdomen and pelvis	An imaging test that uses x-rays taken from different angles. A computer then combines the images to create detailed views of the inside of the body.
Echocardiogram (Echo)	A procedure used to check how well your heart is working. It uses high-frequency sound waves to display pictures of the heart.
Electrocardiogram (EKG or ECG)	A procedure used to show the electrical activity of the heart, using sensors
Endoscopy	A procedure to examine the digestive tract (esophagus, stomach and first part of the small intestine) using a thin, flexible tube with a light and camera
MRI (magnetic resonance imaging) of the brain and heart	An imaging test using radio waves and powerful magnets to create detailed images of the inside of the body
PET/CT (positron emission tomography/computed tomography) scan	An imaging test that uses a radioactive substance called a "tracer" to look for collections of cancer cells (tumors) in the body
Pulmonary function tests	A group of tests that measure how well the lungs are working
Skeletal survey	A series of x-rays that includes the entire skeleton
Ultrasound	An imaging test using high-frequency sound waves to create images of the inside of the body
X-ray imaging	A procedure using high-energy radiation to take pictures of areas inside the body

Visit www.LLS.org/booklets to view *Understanding Lab and Imaging Tests* and *Understanding Genetics* for more information.

To help you visualize and better understand certain tests and processes, visit www.LLS.org/3D to view the interactive 3D model library.

In addition to their hematologist-oncologist (the doctor who specializes in treating cancers of the blood), patients may visit with one or more other specialist doctors including the following:

- Dermatologist, for diseases of the skin
- Endocrinologist, for conditions related to glands and hormones
- Pulmonologist, for disorders of the lungs and respiratory system
- Neurologist, for disorders of the nerves and nervous system
- Ophthalmologist, for diseases of the eye
- Gastroenterologist, for disorders of the digestive system
- Dentist or periodontist, for conditions that affect the teeth and gums

Consultations with providers in other areas, such as smoking cessation, pain management, palliative (supportive) care, and mental health care, may also be recommended.

Treatment

Taking part in a clinical trial may be the best treatment choice for some patients. A clinical trial is a carefully controlled research study conducted by doctors to improve the care and treatment of people who have cancer. Ask your healthcare team if participating in a clinical trial is a good option for you. Read more about clinical trials on page 6.

The US Food and Drug Administration (FDA) approves drugs to treat certain health conditions. **Cobimetinib (Cotellic®)** is the first FDA-approved drug for LCH patients.

Drugs that are not FDA-approved to treat LCH can be used as an "off-label" treatment. "Off-label" prescribing is when a doctor gives a drug that is FDA-approved to treat one condition for another condition, if the doctor feels it will benefit the patient. This is a common practice.

The healthcare team will work with you to determine your best treatment options, based on your individual circumstances. The treatments described below may be used alone or in combination with other therapies.

Single-System LCH. For patients with single-system Langerhans cell histiocytosis (LCH) and no involvement of critical organs, treatment options are listed below.

If LCH is only in the bone:

- Surgical removal of the abnormal tissue (called "curettage")
- Radiation therapy
- Bisphosphonate therapy (drugs that prevent the loss of bone density). Some studies show that bisphosphonates can ease symptoms and improve healing when used with surgery or radiation therapy. Examples of bisphosphonates include **pamidronate (Aredia®)** and **zoledronic acid (Reclast®)** or **(Zometa®).**
- Corticosteroids (hormones produced by the body or in the laboratory primarily to reduce inflammation), given by injection
- Observation (also called "watch and wait"), when there are no other symptoms

If LCH is only in the skin:

- Topical therapy such as **mechlorethamine gel (Valchlor®)**
- Corticosteroids applied topically or given by injection
- **Psoralen** plus UVA or narrow-band UVB (UVA and UVB are types of ultraviolet light; psoralen is a drug taken by mouth or applied to the skin that becomes active when it is exposed to ultraviolet light)
- Surgery for single skin lesions
- Systemic therapy (treating the entire body, such as with chemotherapy) if the patient has pain, infection or other complications
- Observation

If LCH is located in other parts of the body:

- Surgical removal of the abnormal tissue (curettage)
- Radiation therapy
- Observation

Single-system pulmonary LCH (PLCH). For patients with single-system pulmonary (in the lungs) LCH, treatment options include:

- Observation
- Smoking cessation
- Corticosteroids such as **prednisone (various brands)**
- Systemic therapy such as chemotherapy
- Lung transplant

Multi-System LCH (or Single-System LCH with Critical Organ Involvement or Multiple Sites). For patients with multi-system disease, if there are no symptoms and there is no concern about organ dysfunction, observation can be a treatment option.

For those with symptoms or expected organ dysfunction, or involvement of the central nervous system, systemic therapy is recommended. Systemic therapy treats the entire body and may include chemotherapy and other types of medications.

Chemotherapy. Chemotherapy uses drugs to damage the DNA (deoxyribonucleic acid) or RNA (ribonucleic acid) in cancer cells and to interfere with their ability to grow or multiply. Examples are:

- **Cladribine (Leustatin®)**
- **Clofarabine (Clolar®)**
- **Cyclophosphamide (Cytoxan®)**
- **Cytarabine (Cytosar-U®)**
- **Hydroxyurea (Hydrea®)**
- **Lenalidomide (Revlimid®)**
- **Mercaptopurine (Purinethol®, also known as 6-MP)**
- **Methotrexate (various brands)**
- **Thalidomide (Thalomid®)**
- **Vinblastine (Velban®)**

Corticosteroids. Corticosteroid drugs are hormones made in the adrenal cortex (part of the adrenal gland in the body) or manufactured in a laboratory. They are used for numerous purposes in the treatment of cancer. Corticosteroids can decrease inflammation, alter the body's normal immune system responses, cause programmed cell death and stimulate appetite. Chemotherapy often includes the use of a corticosteroid such as **prednisone (various brands).**

BRAF Inhibitors. BRAF inhibitors are drugs that block the action of the *BRAF* V600E protein, which is involved in cell signaling, cell growth and cell division. Examples are:

- **Vemurafenib (Zelboraf®)**
- **Dabrafenib (Tafinlar®)**

MEK Inhibitors. MEK inhibitors are drugs that block the proteins called MEK1 and MEK2. They help control cell growth and survival. Examples are:

- **Cobimetinib (Cotellic®),** taken by mouth, is FDA-approved as a single agent for the treatment of adult patients with histiocytic neoplasms.
- **Trametinib (Mekinist®)**

Hematopoietic Stem Cell Transplant (HSCT). Stem cell transplantation, sometimes referred to as a "bone marrow transplant," is a procedure in which a patient receives healthy stem cells to replace damaged stem cells. Stem cells are special cells produced by the bone marrow that grow to become our blood cells. Autologous (using the patient's own stem cells) or allogeneic (using donor stem cells) transplant may be considered in rare cases of LCH, for patients in which the disease does not respond to treatment or returns after treatment. With the availability of other therapies, the role of HSCT in LCH is less clear at present.

Visit www.LLS.org/booklets to view *Blood and Marrow Stem Cell Transplantation* for more information.

Even after treatment, LCH can continue to grow or spread. This is called "progressive disease." If the disease does not respond to initial treatment, it is called "refractory" LCH. Disease that comes back after treatment is called "recurrent" or "reactivated" LCH. Patients with multi-system disease are more likely to experience a recurrence.

Treatment Side Effects

Side effects depend on many factors, including the type of treatment and dosage, the patient's age, and co-existing medical conditions. Treatment may cause fever or chills, fatigue, nausea, loss of appetite, mouth sores, peripheral neuropathy (tingling, burning, numbness or pain in the hands and/or feet), changes in blood cell counts, infection, rash, vomiting, diarrhea, shortness of breath, swelling, temporary loss of hair, and other side effects.

Side-effect management is important. If you have any concerns about potential side effects, talk to the members of your healthcare team to get help. Most side effects can be managed without compromising the effectiveness of your treatment. In fact, talking to your healthcare team about your side effects often leads to better treatment outcomes. Most side effects are temporary and resolve when treatment is completed. However, long-term side effects or "late effects" may appear years after the treatment has been completed. Late side effects may include development of another type of cancer, heart disease, hypothyroidism (low levels of thyroid hormones), and loss of fertility. See page 8 for more information about specific long-term and late side effects of LCH.

Clinical Trials for Blood Cancers

Every new cancer drug goes through a series of carefully controlled research studies before it can become part of standard cancer care. These research studies are called "clinical trials" and they are used to find better ways to care for and treat people who have cancer. In the United States, the FDA requires that all new drugs and other treatments be tested in clinical trials before they can be used. At any given time, there are thousands of cancer clinical trials taking place. Doctors and researchers are always looking for new and better ways to treat cancer.

Researchers use cancer clinical trials to study new ways to:

- Treat cancer using
  - A new drug
  - A drug that has been approved, but to treat a different kind of cancer
  - A new combination of drugs
  - A new way of giving a drug—by mouth, intravenously (IV), etc.
- Manage cancer signs and/or symptoms and ease treatment side effects
- Find and diagnose cancer
- Keep cancer from coming back (recurring) after treatment
- Manage long-term side effects

By taking part in a clinical trial, patients can see doctors who are experts in their disease, gain access to new, cutting-edge therapies, and provide helpful information for future patients. The treatments and information we have today are due in large part to patients being willing to join clinical trials. Anyone interested in being part of a clinical trial should talk to their hematologist-oncologist about whether a clinical trial might be right for them. During this conversation it may help to:

- Have a list of questions to ask about the risks and benefits of each trial (visit www.LLS.org/WhatToAsk for lists of suggested questions)
- Ask a family member or friend to go with you when you see your doctor—both for support and to take notes

Clinical trials can be difficult to understand and to navigate, but The Leukemia & Lymphoma Society is here to help. Patients and caregivers can work with **Clinical Trial Nurse Navigators** who will help find potential clinical trials, overcome barriers to enrollment and provide support throughout the entire clinical-trial process. Our Clinical Trial Nurse Navigators are registered nurses who are experts in blood cancers and clinical trials. Your

Clinical Trial Nurse Navigator will:

- Talk with you about your treatment goals
- Help you understand the clinical-trial process, including your rights as a patient
- Ask you for details about your diagnosis (such as past treatments, treatment responses, and your cancer genetic profile), your current health and your medical history, because these might impact whether you can take part in certain clinical trials
- Help you understand how your finances, insurance coverage, support network, and ability and willingness to travel might impact your choice of clinical trials
- Guide and help you in your efforts to find and enroll in a clinical trial, including connecting you with trial sites
- Help deal with any problems you might have as you enroll in a trial
- Support you throughout the clinical-trial process

Please call an LLS Information Specialist at (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials and the Clinical Trial Support Center at LLS.

Also, visit www.LLS.org/booklets to view *Understanding Clinical Trials for Blood Cancers.*

Incidence, Causes and Risk Factors

Langerhans cell histiocytosis (LCH) is the most common type of histiocytosis. Histiocytosis is a group of rare disorders in which too many immature histiocytes (a type of white blood/immune cell) build up in certain tissues and organs, including the skin, bones, spleen, liver, lungs and lymph nodes. This can cause damage to tissue or abnormal masses to form in one or more parts of the body.

While LCH is the most common type of histiocytosis, it is considered a rare disease. It may be under-diagnosed or misdiagnosed. LCH is diagnosed in children more frequently than adults. There are approximately 5 to 9 cases per 1 million children younger than age 15 (it is found most often in children ages 1 to 3) and 1 to 2 cases per million adults older than age 15.

According to the Histiocytosis Association, an estimated 63% of adults have lung-only disease (single-system pulmonary LCH), and 90%-95% of these adults are past or current smokers. Most cases of PLCH occur in young adults between the ages of 20 and 40 years.

LCH is associated with mutations in the *BRAF, MAP2K1, KRAS, NRAS* and *ARAF* genes of the histiocytic cells.

The *BRAF* V600E mutation is found in more than half of all LCH cases. These mutations lead to activation of the MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) pathway. The mutations give the cells instructions to make a protein that tells the cells to grow and divide uncontrollably.

A “risk factor” is anything that increases a person’s chance of developing a disease. However, having a risk factor does not mean that a person *will* develop the disease. Some people with several risk factors never develop the disease, while others with no known risk factors may develop the disease.

The National Cancer Institute (NCI) lists possible risk factors for LCH. These factors are suspected but not confirmed:

- Having a parent who was exposed to certain solvents (substances such as benzene from auto emissions or tobacco smoke; paint thinner)
- Having a parent who was exposed to metal, granite, or wood dust in the workplace
- Having a family history of cancer or LCH
- Having a personal history or family history of thyroid disease
- Having infections as a newborn
- Smoking, especially in young adults
- Hispanic heritage
- Not being vaccinated as a child

In pulmonary LCH, it is thought that cigarette smoking causes the activation and accumulation of Langerhans cells (histiocytes) in the lungs, leading to inflammation and injury. For a subset of patients, PLCH may be caused by genetic mutations.

LCH is not contagious (infectious). There is no way to prevent LCH.

LCH can occur along with other types of histiocytosis, such as Erdheim-Chester disease (ECD) or Rosai-Dorfman disease (RDD). While patients with ECD most commonly experience pain in the long bones of the arms and legs, it can affect other parts of the body. In RDD, the histiocytes most commonly accumulate in the neck, although other lymph nodes and parts of the body may also be affected.

Similarly, LCH can be associated with another blood cancer or solid tumor cancer.

LCH in Children

Children with LCH have single-system disease in about 55% of cases. Multi-system disease occurs in the remaining 45% of cases, and most often in children younger than age 3. LCH in children most commonly involves the bones (about 80% of cases), followed by the skin, then the other organs.

Visit www.LLS.org/FamilyWorkbook to find additional information about long-term and late effects (in the chapter titled "Beyond Treatment").

Central Nervous System (CNS) LCH

Central nervous system (CNS) LCH can present as neurodegenerative disease (the cells of the CNS stop working or die, causing decreased mental function) and/or lesions that involve any part of the brain. Diabetes insipidus is the most common disease to be diagnosed first, affecting one-quarter to one-half of patients who have CNS LCH. Diabetes insipidus is an imbalance of fluids in the body that produces large amounts of urine and causes extreme thirst.

Pulmonary (Lung) LCH

Symptoms of PLCH include cough, shortness of breath, fatigue and chest pain. Less commonly, patients have a collapsed lung or lesions seen on a chest x-ray. More than 90% of patients have a history of smoking. Stopping smoking is the primary treatment. Additional treatments may include corticosteroids, chemotherapy or lung transplantation.

Long-Term and Late Effects

Long-term effects of cancer treatment are medical problems that last for months or years after treatment ends. Late effects are medical conditions that do not appear until years, or even possibly decades, after treatment ends.

Long-term and late effects occur in many people with LCH. Patients with multi-system disease are more likely to have one or more long-lasting effects. Children who get LCH are more at risk for these types of effects because LCH can interfere with growth and development. Possible long-term and late effects include:

- Diabetes insipidus
- Skeletal deformities, bone or skull defects
- Stunted growth, loss of height
- Dental issues (eg, loss of teeth)
- Bulging of the eyes
- Hearing loss
- Scarring of the skin, liver or lungs
- Secondary cancers
- Poor coordination and balance
- Memory problems
- Learning difficulties
- Behavior issues
- Chronic pain
- Fatigue

Please visit www.LLS.org/SurvivorshipWorkbook to view the free LLS survivorship publications *Navigating Life During and After a Blood Cancer Diagnosis,* with versions for Adults, Young Adults, and Children and Adolescents.

Follow-Up Care and Monitoring

It is important for patients with LCH to keep all follow-up appointments, to report any health changes to their healthcare team, and to be carefully monitored for disease recurrence, long-term or late effects.

The National Comprehensive Cancer Network (NCCN) is an alliance of leading cancer centers devoted to patient care, research and education. NCCN has developed Clinical Practice Guidelines for healthcare providers who treat LCH. It includes the recommendations for patient follow-up care and monitoring listed below.

Follow-up care may include x-rays and other imaging tests of involved sites to check treatment response after:

- 2 to 3 cycles of therapy
- Completion of therapy
- Completion of a surgical procedure
- Radiation therapy

Monitoring for patients who have had LCH includes:

- Medical history, physical examination, laboratory studies as clinically indicated

- Imaging (PET/CT, CT, or MRI scans)
  - Every 3 to 6 months for the first 2 years after completing treatment
  - After 2 years, no more than annually
  - For patients with a single-site bone lesion and no symptoms, imaging may end after the first year with continued monitoring
- Pulmonary function testing for PLCH
- Bone marrow evaluation if patient has low blood counts or blood abnormalities
- Regular skin examination
- Electrocardiogram (EKG or ECG) for patients treated with BRAF inhibitors
- Monitoring every 1 to 2 years for pituitary hormone abnormalities (eg, diabetes insipidus)

Outcomes

A patient's predicted future outcome (called "prognosis") will depend on the disease presentation, organ involvement and response to treatment. The bone marrow, liver, spleen and central nervous system (called "critical organs") are considered risk organs.

In general, patients with single-system disease or multi-system disease without risk organ involvement are considered low risk. The prognosis is good if the disease is restricted to the skin, lymph nodes or bones, and the patient is over 2 years old.

Patients with multi-system disease with risk organ involvement are considered high risk. Complications and recurrences are more likely when there is involvement of the bone marrow, liver, spleen or central nervous system, or if the patient is under 2 years old.

While LCH has high survival rates, the disease recurs in about one-third of patients. Patients may develop long-term side effects such as diabetes insipidus, bone defects or nervous system problems. In some cases, the disease may go away with appropriate treatment.

Patients with LCH have a higher-than-normal risk of developing secondary cancers.

Tremendous progress has been made in understanding the biology of LCH in the last decade. Ongoing research will surely improve treatment options and effective management of LCH in the future.

Acknowledgement

The Leukemia & Lymphoma Society appreciates the review of this material by:

Gaurav Goyal, M.D.
Assistant Professor
Division of Hematology-Oncology
UAB | The University of Alabama at Birmingham

Feedback

Visit **www.LLS.org/PublicationFeedback** to make suggestions about this booklet.

Health Terms

Diabetes Insipidus. An uncommon disorder that causes an imbalance of fluids in the body. This imbalance leads to the production of large amounts of urine as well as extreme thirst. While the terms "diabetes insipidus" and "diabetes mellitus" sound similar, they are not related. Diabetes mellitus is common and often referred to simply as "diabetes," for which patients take insulin. Diabetes mellitus involves high blood sugar levels and can occur as type 1 or type 2.

Erdheim-Chester Disease (ECD). A rare, slow-growing blood cancer in which an excessive number of histiocytes build up in certain tissues and organs and damage them. ECD most often affects the long bones of the arms and legs, but it can also affect the skin, lungs, heart, kidneys, brain, tissue behind the eyes, and the back wall of the abdomen (called the "retroperitoneum").

Visit www.LLS.org/booklets to view the free LLS fact sheet *Erdheim-Chester Disease*.

Histiocyte. This is a type of immune cell found in many organs and tissues. Histocytes help the immune system destroy foreign substances to protect the body from infection.

Histiocytosis. The term for a group of rare disorders in which too many histiocytes (immune cells) build up in certain tissues and organs, including the skin, bones, spleen, liver, lungs, and lymph nodes. This can cause damage to tissue, and/or cause tumors to form in one or more parts of the body. The tumor may be benign (not cancerous) or malignant (cancerous).

Lesion. An area of abnormal tissue caused by injury or disease. A lesion can be benign (not cancerous) or malignant (cancerous).

Rosai-Dorfman Disease (RDD). A rare disease in which the body produces too many histiocytes in the lymph nodes. The histiocytes most commonly accumulate in the neck, although other lymph nodes and parts of the body may also be affected.

Tumor. An abnormal mass of tissue that forms when cells grow and divide more than they should, or do not die when they should. Tumors may be benign (not cancerous) or malignant (cancerous).

We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has regions throughout the United States and in Canada. To find the region nearest to you, visit our website at www.LLS.org/LocalPrograms or contact an Information Specialist at (800) 955-4572.

LLS offers free information and services for patients and families affected by blood cancers. This section lists various resources you may find helpful.

For Help and Information

Consult with an Information Specialist. Information Specialists can assist you through cancer treatment, financial and social challenges and give accurate, up-to-date disease, treatment and support information. Our Information Specialists are highly trained oncology social workers and nurses. Language services are available. For more information, please:

- Call: (800) 955-4572 (Monday through Friday, 9 a.m. to 9 p.m. ET)
- Email and Live chat: www.LLS.org/InformationSpecialists

Clinical Trials (Research Studies). Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Pediatric and adult patients and caregivers can work with our Clinical Trial Nurse Navigators who will help find clinical trials and provide personalized support throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

Nutrition Consultations. Schedule a free one-on-one nutrition consultation with one of our registered dietitians who have expertise in oncology nutrition. Consultations are available to patients and caregivers of all cancer types. Dietitians can assist with information about healthy eating strategies, side effect management and more. Please visit www.LLS.org/nutrition for more information.

Free Information Booklets. LLS offers free education and support booklets for patients, caregivers and healthcare professionals that can either be read online or ordered. Please visit www.LLS.org/booklets for more information.

Telephone/Web Education Programs. LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. Please visit www.LLS.org/programs for more information.

Financial Assistance. LLS offers financial support to eligible individuals with blood cancer for insurance premiums, co-pays, and non-medical expenses like travel, food, utilities, housing, etc. For more information, please:

- Call: (877) 557-2672
- Visit: www.LLS.org/finances

Resources for Families. Blood cancer occurs in a small number of children. Families face new challenges, and the child, parents and siblings may all need support. LLS has many materials for families including a caregiver workbook, children's book series, an emotion flipbook, dry erase calendar, coloring books and a coloring app, a school re-entry program, and other resources. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/FamilyWorkbook

Podcast. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit www.LLS.org/TheBloodline for more information and to subscribe, to access exclusive content, submit ideas and topics, and connect with other listeners.

Free Mobile Apps.

- LLS Coloring For Kids™ – Allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit www.LLS.org/ColoringApp to download for free.
- LLS Health Manager™ – Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Visit www.LLS.org/HealthManager to download for free.

Suggested Reading. LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit www.LLS.org/SuggestedReading to find out more.

Connecting with Patients, Caregivers and Community Resources

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Visit www.LLS.org/community to join.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients and caregivers reach out and share information. Please visit www.LLS.org/chat for more information.

Local Programs. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection® Program* (a peer-to-peer support program), local support groups and other great resources. For more information about these programs or to contact your region, please:

- Call: (800) 955-4572
- Visit: www.LLS.org/LocalPrograms

Advocacy and Public Policy. Working closely with dedicated volunteer advocates, LLS's Office of Public Policy elevates the voices of patients to state and federal elected officials, the White House, governors and even courts. Together, we advocate for safe and effective treatments. We pursue policies that would make care more accessible to all patients. And, most of all, we advocate for the hope for a cure. Want to join our work? Visit www.LLS.org/advocacy for more information.

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, please visit www.LLS.org/ResourceDirectory to view the directory.

Additional Help for Specific Populations

Información en Español (LLS information in Spanish). Please visit www.LLS.org/espanol for more information.

Language Services. Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information, please

- Call: the VA (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/AgentOrange

Information for Firefighters. Firefighters are at an increased risk of developing cancer. There are steps that firefighters can take to reduce the risk. Please visit www.LLS.org/FireFighters for resources and information.

World Trade Center Health Program. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get help from the World Trade Center (WTC) Health Program. People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area and those who lived, worked or were in school in that area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time, for example, if you feel depressed every day for a two-week period. For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov and enter "depression" in the search box

Resources

Histiocytosis Association
https://histio.org/
(856) 589-6606

The Histiocytosis Association is dedicated to raising awareness about histiocytic disorders, providing educational and emotional support, and funding research leading to better treatments and a cure. The Association offers information about clinical trials, a physician directory, and a search tool for resources.

National Cancer Institute (NCI)
www.cancer.gov
(800) 422-6237

The National Cancer Institute, part of the National Institutes of Health (NIH), is a national resource center for information and education about all forms of cancer.

National Comprehensive Cancer Network (NCCN)
https://www.nccn.org/
(215) 690-0300

NCCN is a non-for-profit alliance of 32 leading cancer centers devoted to patient care, research, and education. Visit the website to view the healthcare professional guidelines. (The patient version of NCCN Clinical Practice Guidelines for Histiocytic Neoplasms is not yet available.)

National Organization for Rare Disorders (NORD)
www.rarediseases.org
(800) 999-6673 / (203) 744-0100

The National Organization for Rare Disorders is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. It is committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and service.

References

Go R, Jacobsen E, Baiocchi R. Histiocytic neoplasms - Version 2.2021. NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2021;19(11). https://doi.org/10.6004/jnccn.2021.0053

Goyal G, Tazi A, Go RS, et al. International expert consensus recommendations for the diagnosis and treatment of Langerhans cell histiocytosis in adults. *Blood.* 2022;139(17):2601-2621. https://doi.org/10.1182/blood.2021014343

Gulati N, Allen CE. Langerhans cell histiocytosis: Version 2021. *Hematological Oncology.* 2021; 39(51)(suppl 1):15-23. https://doi.org/10.1002/hon.2857

Histiocytosis Association. Patient & Family Educational Webinar Series – Focus on Adult LCH/PLCH. https://histio.org/ Accessed May 19, 2022.

Kobayashi M, Tojo A. Langerhans cell histiocytosis in adults: Advances in pathophysiology and treatment. *Cancer Science.* 2018;109(12):3707-3713. https://doi.org/10.1111%2Fcas.13817

McClain KL, Goyal G. Clinical manifestations, pathologic features, and diagnosis of Langerhans cell histiocytosis. UpToDate [online]. https://www.uptodate.com/contents/search Accessed September 23, 2022.

Nakamine H, Yamakawa M, Yoshino T, et al. Langerhans cell histiocytosis and Langerhans cell sarcoma: current understanding and differential diagnosis. *Journal of Clinical and Experimental Hematopathology.* 2016;56(2):109-118. https://doi.org/10.3960/jslrt.56.109

National Cancer Institute. Langerhans cell histiocytosis treatment (PDQ)–Health Professional Version. https://www.cancer.gov/types/langerhans/hp/langerhans-treatment-pdq Accessed September 23, 2022.

National Cancer Institute. Langerhans cell histiocytosis treatment (PDQ)–Patient Version. https://www.cancer.gov/types/langerhans/patient/langerhans-treatment-pdq Accessed August 9, 2022.

National Comprehensive Cancer Network. Histiocytic neoplasms. NCCN Clinical Practice Guidelines in Oncology – Version 1.2022. Accessed August 8, 2022. [Log in required]. https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf

Radzikowska E. Pulmonary Langerhans' cell histiocytosis in adults. *Via Medica – Advances in Respiratory Medicine.* 2017;85:277-289. https://journals.viamedica.pl/advances_in_respiratory_medicine/article/view/ARM.a2017.0046/42214

Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. *Blood.* 2020;135(16):1319-1331. https://doi.org/10.1182/blood.2019000934

Salama HA, Jazieh AR, Alhejazi AY. Highlights of the management of adult histiocytic disorders: Langerhans cell histiocytosis, Erdheim-Chester disease, Rosai-Dorfman disease, and hemophagocytic lymphohistiocytosis. *Clinical Lymphoma, Myeloma & Leukemia.* 2020;21(1): e66-e75. https://doi.org/10.1016/j.clml.2020.08.007

Thacker NH, Abla O. Pediatric Langerhans cell histiocytosis: state of the science and future directions. *Clinical Advances in Hematology & Oncology.* 2019;17(2):122-131. https://www.hematologyandoncology.net/ and place the title of this article in the search box.

Tillotson CV, Anjum F, Patel BC. Langerhans cell histiocytosis. National Library of Medicine: Stat Pearls [Internet] — Continuing Education Activity. May 1, 2022. https://www.ncbi.nlm.nih.gov/books/NBK430885/

This publication is designed to provide accurate and authoritative information about the subject matter covered. It is distributed as a public service by The Leukemia & Lymphoma Society (LLS), with the understanding that LLS is not engaged in rendering medical or other professional services. LLS carefully reviews content for accuracy and confirms that all diagnostic and therapeutic options are presented in a fair and balanced manner without particular bias to any one option.