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LCH is a rare and often underdiagnosed histiocytic disorder with an unknown etiology.

Langerhans Cell Histiocytosis

Nanette Grana, MD

Background: *Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder of unknown etiopathogenesis. Its clinical presentation is variable and ranges from isolated skin or bone disease to a life-threatening multisystem condition. LCH can occur at any age but is more frequent in the pediatric population. A neoplastic origin of this disease has been suggested due to the discovery of the mutually exclusive activating somatic* BRAF *V600E and* MAP2K1 *gene mutations that occur in about 75% of patients.*

Methods: *A survey of recent literature focused on the diagnosis, management, and prognosis of Langerhans cell histiocytosis. Data were collected, analyzed, and discussed with an emphasis on contemporary clinical practice.*

Results: *LCH is common in the pediatric population; compared with adults, children usually have a more aggressive clinical course that requires systemic chemotherapy. Patients with low-risk LCH have an excellent prognosis and a long-term survival rate that may be as high as 99%; by contrast, patients with high-risk LCH have a survival rate close to 80%. Typically, adult patients present with limited skin or bone involvement that can be treated with surgical resection or focal radiation therapy, resulting in an overall survival rate of 100%. Smoking cessation can result in the improvement of respiratory symptoms and the spontaneous resolution of pulmonary LCH. Targeted therapy with BRAF inhibitors has been used in select patients with LCH, and the results have been encouraging.*

Conclusions: *Our understanding of LCH has improved in the last 20 years. Available treatment regimens can control the disease in the majority of patients. The discovery of novel driver mutations and the development of targeted therapy promise better outcomes with fewer long-term therapy-related adverse events, particularly for pediatric and adolescent patients.*

From the Division of Hematology/Oncology, All Children's Hospital, St Petersburg, Florida.

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Address correspondence to Nanette Grana, MD, All Children's Hospital, 501 6th Avenue South, St Petersburg, FL 33701. E-mail: ngrana1@jhmi.org

Introduction

Histiocytic disorders are composed of a group of diverse disorders with a common primary event, ie, the accumulation and infiltration of monocytes, macrophages, and dendritic cells in the affected tissues. Langerhans cell histiocytosis (LCH), a dendritic disorder, is believed to affect fewer than 1 in 200,000 children; however, any age group can be affected.[1] LCH is the result of the clonal proliferation of immunophenotypical and functionally immature LCH cells, as well as eosinophils, macrophages, lymphocytes, and, occasionally, multinucleated giant cells.[2,3] Other terms for

LCH include histiocytosis X, eosinophilic granuloma, Letterer–Siwe disease, and Hand–Schüller–Christian disease; however, the preferred term is LCH because the pathological histiocyte common to all of these diagnoses was identified via electron microscopy to have characteristic Birbeck granules identical to those of the Langerhans cell found in the dermal–epidermal junction of the skin.[4] Additional research has shown that the pathological histiocyte has the gene expression profile of a myeloid-derived precursor dendritic cell, not the Langerhans cell in the skin.[5]

Controversy exists regarding whether the clonal proliferation of LCH cells results from a malignant transformation or is the result of an immunological stimulus.[6] Regardless of the mechanism responsible for the clonal proliferation, the primary treatment, if necessary, involves chemotherapeutic agents. Select chemotherapeutic drugs also have immunomodulatory activity.

The nomenclature of histiocytic disorders has changed in the last 50 years. The current nomenclature, which represents combined efforts of the Histiocyte Society and the World Health Organization, separates LCH disorders from non-LCH histiocytic syndromes and malignancies.[7] The nomenclature used for LCH indicates the disease extent, which may involve a single organ system (unifocal or multifocal) or multiple organs (involving a limited number or they may be disseminated[8]; Table 1[9]). Treatment decisions for patients are based on whether low- or high-risk organs are involved and whether LCH presents as a single- or multisystem disease.[8]

Diagnostic Criteria

The diagnosis of LCH is based on a histological and immunophenotypical examination of tissue. The main feature is the morphological identification of the characteristic Langerhans cells. In addition, positive staining of the lesional cells with CD1a, langerin (CD207),

Table 1. — Clinical Classification of Langerhans Cell Histiocytosis

Single System	Unifocal or multifocal organ system involvement
	Unifocal or multifocal bone involvement
	Skin
	Lymph node
	Hypothalamic/pituitary/central nervous system
	Other (eg, thyroid)
Multisystem	Involvement of ≥ 2 organs or systems

From Broadbent V, Gadner H. Current therapy for Langerhans cell histiocytosis. *Hematol Oncol Clin North Am.* 1998;12(2):327-338.© 1998 Reproduced with permission from Elsevier.

or both are required for a definitive diagnosis. The expression of langerin confirms the presence of Birbeck granules, the cytoplasmic organelles typically found in Langerhans cells.[4]

Pathophysiology and Etiology

The diagnosis of LCH is based on hematological and histological criteria established by the Histiocyte Society in 1987.[6] Lesions seen in cases of LCH are polymorphous that typically vary little from site to site and from patient to patient; they also feature a monoclonal population of CD1a^{+} monocytes.

The cause of LCH is unknown. Researchers have debated whether LCH represents a true malignancy or a reactive immune condition.[10] Studies favoring that LCH is a malignancy have demonstrated that LCH cells from nonpulmonary lesions are monoclonal,[2,8] whereas other supportive findings include the immature appearance of lesional LCH, the presence of cell-cycle dysregulation within lesions, and the presence of significant telomere shortening of the LCH cells compared with Langerhans cells from other inflammatory lesions.[11] By contrast, research supporting LCH as a reactive process emphasize that clonal cell populations are commonly present within the immune system and that phenotypically immature Langerhans cells often accumulate in areas of inflammation.[12] The lesional expression of cytokines, most recently interleukin 17, which is a key cytokine in several autoimmune disorders, has been reported.[12]

Badalian-Very et al[13] and Davies et al[14] have provided new insight into LCH, demonstrating that about 50% of studied cases exhibit somatic-activating mutations of the proto-oncogene *BRAF*. The study by Badalian-Very et al[13] described the first molecular abnormality implicated in the pathogenesis of LCH and is important for several reasons. The identification of activating *BRAF* gene mutations strongly supports the hypothesis that LCH is a neoplastic process, at least in some cases. This observation has clinical implications because it suggests that alternative therapeutic approaches aimed at targeting active *BRAF* should be tested in the setting of LCH. Furthermore, this mutation may provide a means to assess the status of minimal residual disease in a subset of patients with LCH. Although the study did not discern whether LCH is a neoplasm or an immune dysregulation, its results provided critical information to move research in the right direction.[13] Brown et al[15] recently reported on the novel somatic *MAP2K1* mutations in approximately 50% of patients with LCH who tested negative for *BRAF* V600E using a next-generation sequencing platform. Most of the mutations were in frame deletions. Mutations in *BRAF* and *MAP2K1* were mutually exclusive, suggesting that *MAP2K1* has an important role in the pathogenesis of LCH. Targeted therapy

with BRAF, MEK1, or ERK inhibitors may change the treatment algorithm of LCH in the near future.

Clinical Presentation
Single System
Skin: Seborrheic involvement of the scalp may be mistaken for prolonged cradle cap in infants. Infants sometimes present with Hashimoto–Pritzker disease (purplish papules on their body), which is also known as congenital self-healing reticulohistiocytosis. This manifestation may be self-limited and oftentimes disappears without therapy. Patients must be closely watched for systemic disease, which may present following the initial appearance of skin lesions.

Children and adults may also develop a red papular rash on their groin, abdomen, back, or chest that resembles a rash caused by *Candida*. They may also develop seborrheic scalp involvement.

Oral Cavity: Lesions in the oral cavity may precede evidence of LCH elsewhere and may include hypermobile teeth, gingival hypertrophy, or ulcers of the mucosa, tongue, or lips.

Bone: Lytic skull lesions are the most common sites of LCH in children, and the lesion may be asymptomatic or painful and is often surrounded by a soft-tissue mass.[16] Other frequently involved skeletal sites are the ribs, humerus, and vertebra.[17] Spine lesions may result in the collapse of the vertebra plana. Orbital sites may be affected; proptosis from LCH of the orbit mimics neuroblastoma or rhabdomyosarcoma.[18]

Pituitary Gland: The posterior part of the pituitary can be affected and may lead to central diabetes insipidus. Involvement of the anterior pituitary may result in a failure to grow and delayed or precocious puberty.

Multisystem Disease
In multisystem LCH, the disease presents in multiple organs or body systems, including bone, the abdomen, the gastrointestinal tract (liver and spleen), lungs, bone marrow, the endocrine and central nervous systems, skin, and the lymph nodes.

Bone and Other Organ Systems: Patients with LCH may present with single- or multisystem, multifocal bone lesions.

Abdomen and Gastrointestinal Tract: In the setting of LCH, the liver and spleen are considered high-risk organs and any disease involvement of these organs affects a patient's prognosis. The liver and spleen may become enlarged due to the direct infiltration of LCH cells or as a secondary phenomenon of excess cytokines, which activate macrophages or infiltrate lymphocytes around the bile ducts. A serious complication of hepatic LCH is sclerosing cholangitis.[19] A total of 75% of children with sclerosing cholangitis will not respond to chemotherapy because LCH is no longer active but fibrosis and sclerosis are still present.[19] Liver transplantation is the only alternate treatment when hepatic function worsens.[19]

Spleen: Massive splenomegaly may lead to cytopenias because of hypersplenism and may cause respiratory compromise. Typically, splenectomy provides transient relief of the cytopenias because the increasing size of the liver and reticuloendothelial activation result in peripheral blood sequestration and destruction. Splenectomy should only be performed as a life-saving measure.

Lungs: Lungs are less frequently involved in children than in adults due in part to smoking, which is a key etiological factor.[20] Tachypnea with rib retractions is often the first and only clinical sign. The cystic/nodular pattern of the disease reflects the cytokine-induced destruction of lung tissue. Pulmonary involvement is present in approximately 25% of children with multisystem LCH.[21]

Bone Marrow: Most patients with bone marrow involvement are young children with diffuse disease in the liver, spleen, lymph nodes, and skin; these patients usually present with significant thrombocytopenia and anemia with or without neutropenia.[22] Patients with LCH who are considered at very high risk may present with hemophagocytosis involving the bone marrow.[10]

Central Nervous System: Neurological problems involving deficits in cognition, as well as behavioral disturbances and neuromotor dysfunction due to central nervous system involvement affect at least 10% of all patients with LCH and 19% of patients with multisystem disease.[23] Within the last 15 years, the knowledge and understanding of the findings on magnetic resonance imaging of the brain in patients with LCH have grown.[24] Classification of central nervous system disease by the Histiocyte Society is referenced in Table 2.[25]

In the hypothalamic pituitary region, the characteristic features seen on magnetic resonance imaging consist of an enlarged pituitary stalk with the potential progression to space-occupying tumors that extend to the pituitary and the hypothalamus. In the setting of diabetes insipidus, typically a "loss of bright spot" can be seen, correlating with the loss of antidiuretic hormone-containing granules. The LCH-associated pineal gland abnormalities comprise solid masses or cystic lesions. Other space-occupying tumorous lesions may occur, although rarely, in the meninges, choroid plexus, and in the brain parenchyma.

Another frequent presentation of LCH involving the central nervous system, excluding hypothalamic pituitary region disease, is a combination of pathological changes in the cerebellum, basal ganglia, and/or pons, with characteristic patterns seen on magnetic resonance imaging. Prosch et al[7] termed this pattern "radiological neurodegeneration."

Table 2. — Classification of Magnetic Resonance Imaging for Langerhans Cell Histiocytosis and Intracranial Lesions

Tumorous/Granulomatous Lesions
Granulomatous lesions of skull bones
Hypothalamic pituitary lesions
Hypothalamus
Anterior pituitary
Choroid plexus

Meninges
  Nontumorous
  Nongranulomatous

Cerebellar white matter
Brainstem/pons
Supratentorial white matter
Atrophy
Cerebellar
Midbrain
Supratentorial

Modified from Grois N, Fahrner B, Arceci RJ, et al. Central nervous system disease in Langerhans cell histiocytosis. *J Pediatr*. 2010;156(6): 873-881, 881.e1. © 2010 Reproduced with permission from Elsevier.

Clinical symptoms depend on the site and the type of involvement within the central nervous system. Diabetes insipidus, which represents the hallmark of infiltration of the hypothalamic pituitary region, is seen in as many as 25% of patients with LCH and as many as 50% of patients with multisystem disease.[26,27]

Tumorous lesions of the meninges or choroid plexus can lead to headaches, seizures, and other focal symptoms as well as the obstruction of the ventricles when intracranial pressure is increased.

LCH-associated neurodegenerative lesions are associated with a highly variable clinical picture.[25] Many patients will be free of neurological symptoms despite typical changes of radiological neurodegeneration that have been seen on magnetic resonance imaging for years. However, other patients may have clinical neurodegeneration, with a spectrum of clinical signs ranging from mild abnormalities of the reflexes, discrete gait disturbances, dysarthria, dysphagia, and motor spasticity to pronounced ataxia, behavioral disturbances, learning difficulties, or severe psychiatric disease.

Therapy

Treatment decisions are based on whether the high- or low-risk organs are involved and whether the disease is single system or multisystem (Fig).

Treatment progress for LCH has benefited from the adoption of standard diagnostic criteria, the standard evaluation of the extent of disease, and stratified treatment.[28] International efforts during the last 20 years have shown that combination therapy with vinblastine/prednisone is an effective therapy for multisystem LCH. Trials conducted by the Histiocyte Society confirmed this regimen as standard therapy for multisystem LCH with and without risk organ involvement.[29,30]

Risk organs and their involvement were defined according to modified Lahey criteria as follows[31]:
- Hematopoietic: Anemia and/or leukopenia and/or thrombocytopenia
- Liver: Enlargement > 3 cm below the costal margin, dysfunction, or both
- Spleen: Enlargement > 2 cm below the costal margin
- Lung: Typical changes via high-resolution computed tomography, histopathological diagnosis, or both

Some cases of LCH have limited involvement and may not require treatment. Treatment of localized skin disease may be unnecessary because, in many cases (typically in infants), the lesions will spontaneously regress. Single bone lesions tend to spontaneously resolve during a period of months to years and may initiate healing after biopsy.

Preliminary data from a trial conducted by the Histiocyte Society suggest that, for multisystem disease, the treatment duration of 12 months reduces the risk of reactivation compared with 6 months of total treatment.[32] Patients with multisystem LCH at diagnosis may have a variable clinical course. Those without risk organ involvement, as well as those with risk organ involvement but who respond to standard initial therapy, have an excellent chance of long-term survival. Combination prednisone/vinblastine has been proven to be an effective treatment with minimal toxicity; therefore, it is the standard initial therapy for all patients in whom systemic therapy is indicated.[30,33] Patients with risk organ involvement who do not respond within the first 6 weeks of therapy, particularly those with evident clinical progression, have an unfavorable prognosis.[28,30,34] For such patients, an early intensification of therapy is justified.

Salvage Therapy
The optimal treatment for relapsed or recurrent LCH has not been determined, although several regimens exist. Patients with recurrent bone disease who have recurrences months after stopping vinblastine/prednisone may benefit from treatment with vinblastine/prednisone/mercaptopurine.[35] Cladribine has also been shown to be effective for recurrent, low-risk LCH.[28] For patients with recurrent or refractory multisystem or multiorgan involvement, few treatment

options exist; however, promising results have been reported with combination cladribine/cytarabine[36] and stem cell transplantation.[37]

Pediatric Population

The reported overall incidence of the long-term consequences of LCH ranges from 20% to 70%. The reason for this wide variation is due to sample size, therapy used, duration of follow-up, and method of data collection.[38] Children at low risk for organ involvement have approximately a 20% likelihood of developing long-term sequelae.[38] Patients with multisystem involvement have a 71% likelihood of developing long-term problems.[38-41] The most commonly reported permanent consequences are diabetes insipidus, orthopedic abnormalities, hearing loss, and neurological issues.
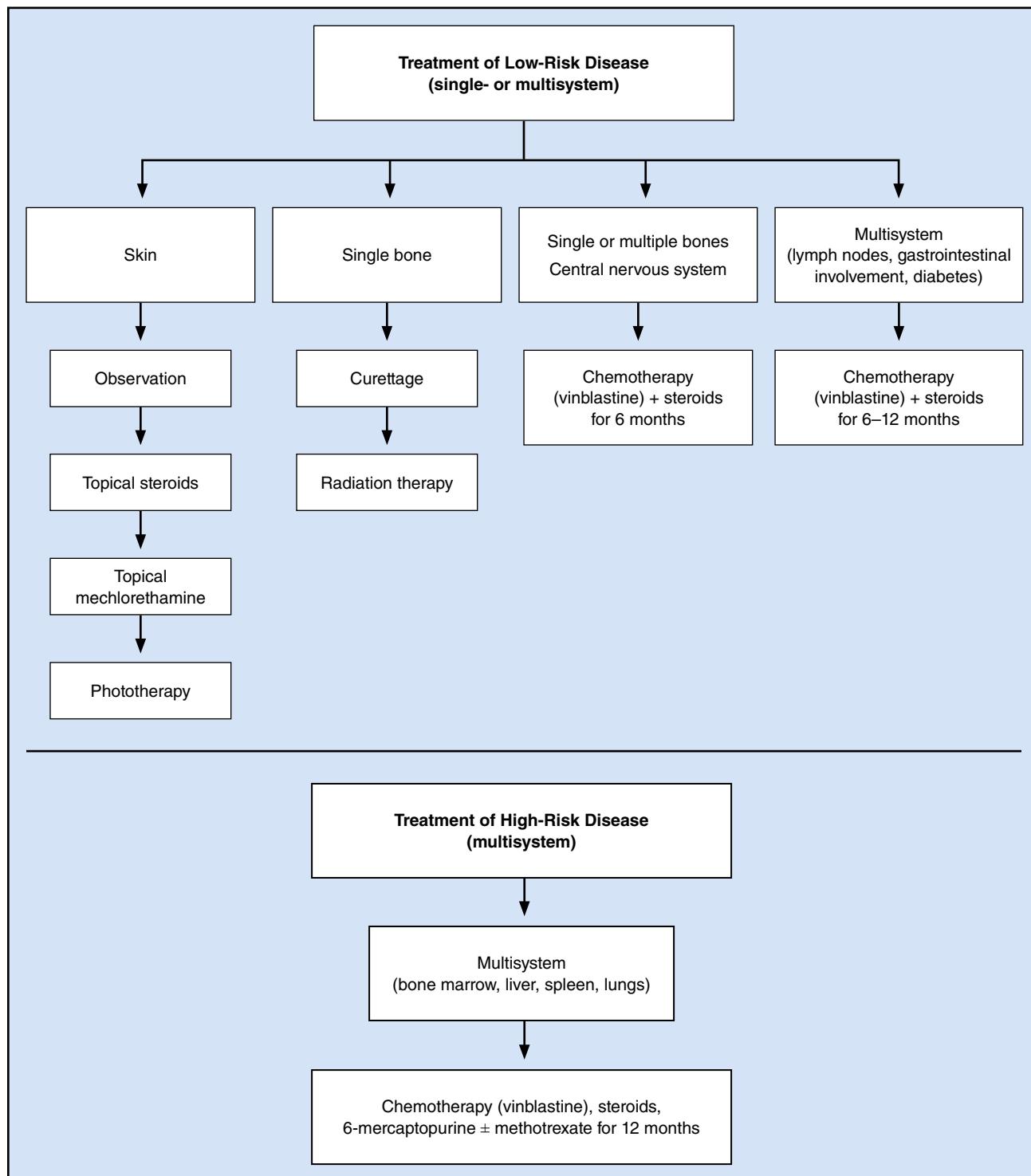

Fig. — Treatment algorithm for childhood Langerhans cell histiocytosis.

Patients with reactivations or chronic disease may experience severe permanent consequences that reduce their quality of life, particularly when the disease affects the central nervous system, the lungs, or leads to hormone deficiencies, neurodegenerative syndrome, and lung fibrosis, among other issues.[19]

Adult Population

With the exception of pulmonary LCH, the natural history of the disease among adults is unknown. It is estimated that 1 to 2 adult cases of LCH occur per 1 million people[42]; however, the true incidence is unknown because this disorder is often underdiagnosed. Adults with LCH may have symptoms and signs for months before receiving a definitive diagnosis. In addition, predominance of lung disease exists in adults with LCH.[43] The lack of clinical trials limits the ability of health care professionals to make evidence-based recommendations for adult patients with LCH.

Prognosis

A recent review of the Surveillance, Epidemiology, and End Results database revealed that 828 US pediatric cases with histiocytoses had been diagnosed between 1973 and 2010 and an improved survival rate was seen during the last 40 years.[44]

In a large national survey study from South Korea, 603 patients with LCH were identified between 1986 and 2010. The majority of patients (69.5%) presented with single-system involvement, 14.1% with multisystem disease without risk organ involvement, and 16.4% with multisystem disease with risk organ involvement. The 5-year overall survival rates in all 3 prognostic groups were 99.8%, 98.4%, and 77.0%. Long-term adverse events of therapy were identified in 16.4% patients.[45]

In a prospective clinical study from Japan, 91 patients with LCH were treated with a combined chemotherapy regimen between 1996 and 2001.[46] Five-year overall survival rates for patients with single-system multifocal and multisystem disease were 100% and 94.4%, respectively.[46]

In a single institutional, retrospective study from Italy, 121 patients with LCH were treated between 1968 and 2009.[47] The overall survival rate of the group at 10 years was 93%. Patients 2 years or younger had a worse prognosis; their overall survival rate was 82% compared with 97% for patients older than 2 years. Patients with multisystemic disease with risk organ involvement also had worse outcomes compared with patients without risk organ involvement.[47]

Altogether, the above data suggest that the prognosis of patients with LCH has improved within the last 40 years following the advent of modern chemotherapy regimens. Despite excellent outcomes observed in the majority of patients, LCH can be fatal in up to 20% of patients, particularly among those with multisystem risk organ involvement and age younger than 2 years.

Conclusions

Langerhans cell histiocytosis is a rare disease. In the United States, researchers believe that the disease goes underdiagnosed. It is most commonly seen in young children, but any age group can be affected.[1] The cause of the disease is unknown, although the possibilities of the malignant transformation of the myeloid progenitor precursor of Langerhans cell histiocytosis and immune dysregulation are being explored.[2-4] Recent discoveries of driver mutations in *BRAF* and *MAP2K1* genes could change the therapeutic armamentarium in Langerhans cell histiocytosis from chemotherapy to targeted therapy, resulting in a better prognosis and a lower rate of long-term therapy-related adverse events.

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