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Review Article

**LANGERHANS CELL HISTIOCYTOSIS: STORY OF THE
ORPHAN DISEASE BEYOND DERMATOLOGY****Latifa Alanazi^{1*}, Ghada Alhindi¹, Yara Alanazi¹, Sarah Alseneidi¹, Bashayer
Alanazi², Dalal Alshagha¹, Munira Alghufaily¹, Nada Dammas¹**¹College of Medicine, King Saud University, Riyadh, Saudi Arabia, ²Pediatric Department,
King Abdulaziz Medical City, Riyadh, Saudi Arabia.**Abstract:**

Langerhans cell histiocytosis (LCH), a rare proliferative disorder of cells that share phenotypic characteristics with dermal Langerhans cells, has long been considered an "orphan," or neglected disease. Prior to its current designation, LCH was known as Hand-Schuller-Christian disease, Letterer-Siwe disease, or eosinophilic granuloma, which was combined under the umbrella designation of Histiocytosis X. The pathogenesis of LCH has remained unclear since the initial reports approximately 100 years earlier, and gene expression studies have demonstrated that these tumors do not originate from dermal Langerhans cells. It remains unclear whether LCH is reactive or neoplastic, although these tumors manifest a unique self-healing phenomenon that is rare among malignancies. The clinical presentation of LCH varies according to the involved organ/system, including common manifestations such as otitis media or pneumothorax or unusual manifestations such as diabetes insipidus. Accordingly, LCH cases are classified according to the number of involved organs/systems and sites, as well as the involvement of so-called "risk organs". This review aimed to highlight recent insights as a better understanding of LCH will lead to more effective therapies.

Key words: *Langerhans cell histiocytosis, Histiocytosis X, Hand-Schuller-Christian disease, Letterer-Siwe disease, Orphan disease.*

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INTRODUCTION:

Langerhans cell histiocytosis (LCH) is a rare clonal disorder characterized by an accumulation of CD1a-positive immature dendritic cells (i.e., LCH cells) [1], which exhibit several main phenotypic features associated with epidermal Langerhans cells [2], including the expression of Langerin (CD 207) [3]. Despite the rarity of LCH, it is known as the most common of the human histiocytic disorders [4], a family of rare diseases characterized by the accumulation of macrophages, dendritic cells, or monocyte-derived cells in different tissues and organs in both children and adults [5].

Current reports estimate the pediatric incidence of LCH as 9 cases per million children younger than 15 years, or similar to the incidence of pediatric Hodgkin lymphoma [6, 7]. Among adults, the

incidence of LCH is approximately 1 case per million [5]. Two independent studies conducted in France and Japan estimated an annual incidence of LCH of 1 case per 200,000 subjects at risk [8]. Regarding demographics, LCH appears to be more common among boys than among girls (sex ratios of: 1.2–2:1) [1], among individuals of with a Caucasian genetic background than among those with an African genetic background, and among those of Hispanic ethnicity than among non-Hispanics [9]. In both children and adults, LCH manifests as a wide spectrum of clinical presentations, ranging from self-limited lesions to life-threatening disseminated disease [5]. Accordingly, LCH has been known by several different names, although the lesions share a common histopathological appearance (**Table - 1**) [10].

Table – 1: Classification and prevalence of LCH entities

Classification		Prevalence
Present	Former	Among LCH [1]
High Risk Organ Involvement		Letterer–Siwe disease [51]
Low Risk organ Involvement	Multisystem	Hand–Schüller–Christian disease [2]
	Single-system	Eosinophilic granuloma [2]
		70%

As noted in the previous paragraph, LCH can occur at any age but predominantly affects children [11]. Among pediatric cases, the most commonly affected organs include the bones (80% of cases), followed by the skin (33%); pituitary gland (25%); liver, spleen, bone marrow, or lungs (15% each); lymph nodes (5–10%); and non-pituitary central nervous system (CNS; 2–4% of cases). In contrast to the patterns observed among pediatric LCH cases, in adult cases, the most commonly affected organ is the lung [12], and the incidence has been shown to correlate with cigarette smoking [1, 13]. However, LCH can affect any organ [5, 14]. Among cases involving the bone, the skull is most frequently affected in children, whereas cases involving the jaw are more common among adults [1]. Again, however, any bone may be involved [15].

LCH lesions may be painless or painful [15], and the presentations vary [10]. The liver, bone marrow, and spleen are considered organs-at-risk [14, 16, 17], as the involvement of these organs is thought to correlate with a worse prognosis [17]. Additionally, some reports have included the lungs as organs-at-risk [18, 19], although the individual prognostic effect of lung involvement has recently been questioned [14]. Anemia, leukopenia, and/or thrombocytopenia are also considered signs of high risk organ involvement [18]. Clinically, LCH can be

classified as either single-system or multisystem disease [16, 20]. The former category can be subdivided further as unifocal (one lesion) or multifocal (multiple lesions involving the same system or organ), whereas the latter category can be further classified according to the involvement (or not) of the high risk organs [20]. Currently, the low risk organ involvement, single-system LCH is considered prototypical (**Table - 1**) [1].

In 1987, the Histiocyte Society Writing Group outlined the following diagnostic criteria for LCH: classical LCH histopathology confirmed by the detection of Birbeck granules (BG) via electron microscopy (EM) or the demonstration of CD1a positivity via immunohistochemistry [21]. However, the EM-based detection of BG has since been replaced with the immunohistochemical detection of CD1a and Langerin (CD207) [5], as the latter has been shown to induce the formation of BG. Accordingly, CD207 is considered a marker indicative of the presence of BG [22]. In addition, LCH cells are positive for S100 protein

[17] and generally co-express CD14, CD36, CD80, and CD86 [2], with variable expression of CD68 [17]. Histologically, Rizzo, et al. reported that LCH lesions contain several types of cells, including LCH

cells (36–58%), T cells (13–18%), macrophages (2–30%), eosinophils (1–10%), rare B cells (1–3%), and multinucleated giant cells [2].

The diagnosis of LCH can be challenging, as these lesions tend to mimic more common conditions, such as otitis media [21], and may present with variable symptoms [10]. Chronic ear infections accompanied by a yellow discharge in the external ear canals and/or tooth loss with gingival swelling are characteristic of LCH and should raise concerns [12]. Similarly, a new onset of diabetes insipidus should raise suspicions regarding LCH involving the pituitary gland [12].

Against the above background, the present review aims to highlight recent insights regarding LCH, including reported clinical manifestations and treatments, questions regarding the cell type of origin and pathogenesis of LCH, and other histiocytic entities reported to occur in association with LCH (e.g., juvenile xanthogranuloma; JXG, Erdheim–Chester disease; ECD).

Clinical manifestations

LCH can affect the bones, skin [5], or even the conjunctivae [23], and the clinical manifestations vary greatly according to the affected site, as noted previously [10]. Typically, bone lesions may cause critical symptoms such as a loss of vision, hearing, and/or teeth or even spinal paralysis, which are respectively attributed to involvement of the orbital, mastoid antrum, jaw, and vertebrae [1], although cases that are restricted to the bone may have a benign clinical course with spontaneous resolution [1]. Skin involvement may appear as a scaly, greasy rash, ulcerations with small abscesses [12], or lesions such as papules, erythema, petechiae, nodules, vesicles, crusted plaques, and seborrhea-like eruptions [1].

Pulmonary LCH (PLCH) is a form of interstitial lung disease that is considered distinct from systemic LCH with lung involvement [24]. PLCH can present as dyspnea, a non-productive cough, and pleuritic chest pain [24], and affected patients may develop pneumothorax and/or pulmonary hypertension [24]. In children, PLCH mainly occurs in the context of multisystem disease [1], but has been shown to be associated with cigarette smoking in adults [1, 13]; in the latter, these cases may regress after smoking cessation [1]. However, smoking cessation may be insufficient to disrupt the inflammatory process, and the affected adults may become oxygen dependent [25].

LCH has been associated with a devastating neurodegenerative condition that may develop even decades after the initial presentation [15] or even years after LCH presumed to be cured [26]. The symptoms of LCH-associated neurodegeneration include tremor, ataxia, dysmetria, dysphagia, behavioral changes, and learning disability [15], and characteristic changes in the cerebellum, basal ganglia, and/or pons can be identified radiologically [15, 26]. The pathophysiology of LCH-associated neurodegenerative disease is thought to result from an autoimmune or inflammatory reaction to LCH [15]. However, recent research data by McClain and colleagues [26] support a model of LCH associated neurodegeneration not as a reactive autoimmune or paraneoplastic process, but rather an active neurodegenerative process driven by common BRAFV600E myeloid precursors that are shared with systemic LCH lesion CD207 cells.

Mysterious cell of origin

At present, the exact origin and trigger of LCH remain unclear and under investigation [27]. The current understanding of LCH began to form more than a century ago [27]. Between 1893 and 1919, Alfred and Arthur Chlifer, and Henry Christian independently described cases involving collective symptoms such as exophthalmos, diabetes insipidus, and skull lesions i.e., and Chlifer–Christian disease), which would currently be classified as the single-system, multiple-site variant of LCH [27]. Between 1924 and 1936, Erich Letterer, Sture A. Siwe, and Arthur F. Abt described their experiences with children who exhibited rash, hepatosplenomegaly, anemia, and bone tumors visible on X-rays (i.e., Abt–Letterer–Siwe disease). Such cases resemble the current multisystem variant of LCH [27]. In 1940, Sadao Otani and John C. Ehrlich, as well as Louis Lichtenstein and Henry L. Jaffe, reported patients with solitary bone lesions that were designated as “eosinophilic granulomas” [27].

Subsequently, the pathologic and radiographic similarities of the previously mentioned disease entities were observed, and all three were grouped under the umbrella designation of “histiocytosis X” [27].

During the 1960s, EM facilitated the detection of similarities, such as BG, between the Langerhans cell, a specialized type of dendritic cell found in the skin [28], and the histiocytes observed in

histiocytosis X disease lesions [27]. Accordingly, the Langerhans cell was suggested as the cell of origin of LCH [27], which led to the renaming of histiocytosis X to LCH in 1987 by the Histiocyte Society Writing Group [27]. However, progress in the fields of immunology and molecular biology have improved our ability to compare differences at the molecular level [29], and more recent gene expression studies and other molecular investigations have confirmed that the skin Langerhans cell is not the cell of origin for LCH [28, 30]. Moreover, given previous reports of viral involvement in LCH pathogenesis [1, 15, 16, 31], we should keep in mind that an onco- virus might mask the actual cell of origin [32].

Further studies have proposed that the genetic profile of LCH cells is more similar to that of a bone marrow-derived immature myeloid dendritic cell [12, 15, 18, 27, 30, 33], which also expresses the same antigens as skin Langerhans cells [12]. Despite genetic differences, however, LCH cells are phenotypically similar to skin Langerhans cells in terms of morphology and surface markers expression [34]. In addition to BG, LCH cells express CD1a, Langerin, and S100, but fail to express markers typical of more mature dendritic cells (e.g., CD83) [29]. Microscopically, however, LCH cells exhibit a more rounded appearance relative to skin langerhans cells, and lack dendritic cell extensions [29].

One interesting phenomenon in this context is the development of other histiocytic sequelae after LCH, specifically JXG and ECD. Several cases of JXG subsequent to LCH have been reported in previous decades [35, 36], and JXG was discovered before LCH in a patient discussed by Tran, et al. [37]. In addition, JXG and LCH were discovered simultaneously in cases reported by Shani-Adir, et al. [38] and Hong Yu, et al. [39].

imilarly, “mixed histiocytosis,” a term used to describe the simultaneous presence of LCH cells and ECD in a patient at the same or different sites, was first reported by Hervier, et al. [40], who suggested an association of this condition with the B-rapidly accelerated fibrosarcoma gene (BRAF) V600E mutation (see the following section for further details). Nabi, et al. presented a rare case of ECD and LCH overlap syndrome, in which although the clinical features were consistent with an ECD diagnosis and the radiological studies were pathognomic for ECD, a biopsy confirmed LCH [41].

These rare but well documented events have elicited various questions concerning the pathogenesis and biology of LCH and non-LCH and their correlations

[35]. Notably, these associations might indicate a common origin of LCH and non-LCH [42]. A previous study of the mechanism of GATA-2 dependent myelodysplastic syndrome or MonoMac syndrome development identified a common monocyte and dendritic cell progenitor, thus lending further support to theories regarding a common origin [43].

Is LCH Neoplastic or Reactive?

Similar to the etiology [44, 45], the pathogenesis of LCH remains indefinite [1]. Still, although inflammation, autoimmunity, and a loss of controlled Langerhans cell proliferation have been suggested as etiologic factors [21], the pathogenesis of LCH remains vague [1]. Furthermore, the debate regarding whether LCH represents a true malignancy or a reactive inflammatory condition is longstanding [18, 33,34].

The known involvement of pro-inflammatory cytokines and chemokines in LCH suggests that this is an immune disorder [1]. However, more than half of patients with LCH and nearly 60% of associated lesions harbor the oncogenic BRAF V600E mutation [1, 46], suggesting that LCH is a neoplastic disorder [1,46]. This high prevalence of the BRAF-V600E mutation among LCH cases has been confirmed in several independent cohorts [15]. By contrast, the BRAF-V600E mutation is observed in approximately 7% of human cancers [15], as well as in several benign neoplastic conditions, [6, 15] such as epidermal nevi and colon polyps, and highly aggressive malignancies such as malignant melanoma [6]. The impact of BRAF V600E appears to be dependent on the cellular context [6], and the specific role of this mutation in LCH pathogenesis remains elusive [6].

Several studies have provided favorable evidence to support the designation of LCH as a malignancy. For example, LCH cells have an immature phenotype, and the presence of cell- cycle dysregulation has been observed within lesions [18, 46]. Additionally, LCH cells are more likely to harbor chromosomal alterations, such as significant telomere shortening, when compared with Langerhans cells from other inflammatory lesions [18, 46]. Notably, telomere shortening has been associated with the development of cancers and premalignant lesions, as well as chromosomal instability [44]. Furthermore, the accompaniment of LCH by myelodysplastic syndrome and other malignancies and evidence suggesting the clonality of LCH cells further support a neoplastic origin [15]. However, although clonality

is essential for malignancy [1], clonality alone does not specify malignancy among immune cells [15]. Still, LCH lesions do express classical features of malignancy [4], including tumorigenic mechanisms such as BCL2L1 overexpression, which may contribute to resistance to cell death [4, 6].

An infectious origin of LCH has been suspected but unproven since the nineteenth century [25]. Recently, some DNA sequences corresponding to viruses such as Merkel cell polyomavirus (MCPyV) [15, 16] and Epstein–Barr virus (EBV)

[31] have been identified in the peripheral blood and tissues of patients with LCH [1]. Additionally, human herpesvirus 6 has been identified in LCH lesions [31], thus lending further support to an inflammatory origin. An epidemiologic study identified an increase in infections, the use of antibiotics in the first 6 months of life, and a family history of thyroid disease as risk factors for multisystem-LCH [13]. Moreover, LCH may develop even after some treatments; for example, bladder LCH development has been reported after immunotherapy with intravesical Bacillus Calmette-Guérin (BCG), which modulates the expression levels of several cytokines [47].

Finally, no evidence suggests that LCH cells are immortalized [1].

In contrast, several lines of evidence suggest that LCH is reactive in nature. For example, LCH lesions sometimes regress spontaneously [1]. Spontaneous self-healing, which rarely occurs with neoplasms, is common among LCH cases, suggesting the potential for multiple pathobiologic contributions to the LCH process

[13] Studies that support LCH as a reactive process emphasize that clonal cell populations are frequently present within the immune system [18]. Moreover, the lesional expression of cytokines, particularly interleukin 17, an indispensable cytokine in several autoimmune disorders, has been described [18, 46], thus validating the inflammatory/reactive theory.

Although LCH obviously exhibits characteristics of inflammation, an infectious or autoimmune etiology remains to be confirmed [15]. As noted, recent findings regarding the BRAF V600E mutation frequency [1, 48] and other hallmarks of malignancy [4, 6] have favored a neoplastic etiology. Still, LCH cells are characterized by a “enigm” morphology, with very low mitosis rates similar to those of normal epidermal Langerhans cells [6].

Murakami and others [13] have presented a new

model of LCH pathogenesis which proposes that this disease is a reactive disorder with underlying neoplastic potential [13]. As demonstrated, however, it is very difficult to conclude the true nature of LCH, as a tumor could promote inflammation [6] while chronic inflammation is known to promote oncogenesis [49].

Treatment

In summary, the pathophysiology of LCH still in the process of being clarified, but appears to associate with abnormalities Langerhans cell and macrophage biology [50]. Therefore, the identification of better treatment modalities for LCH will require an understanding of the underlying defects and the developmental process. Currently, treatments for LCH depend on the degree and severity of the disease at the time of diagnosis, and involve approaches such as surgery, chemotherapy, and radiotherapy, either alone or in combination [21]. Patients with single-system involvement are generally treated with surgery, radiation, or local steroid injection [21], although those with single-system LCH with CNS risk lesions or multifocal bone lesions are candidates for systemic therapy [12]. By contrast, patients with multisystem involvement often receive chemotherapy [21], often in combination with local steroid injections [21]. Commonly used cytotoxic agents include vinblastine, methotrexate, etoposide, and mercaptopurine, which are used in combination with prednisolone [21]. Still, more than half of all patients are refractory to vinblastine/prednisone or develop recurrent lesions [4], and disease reactivation remains a significant problem [4].

Despite the existence of several regimens, an optimal treatment has not yet been established [1, 18]. However, recent studies have shown that a longer duration of treatment results in less disease reactivation [33]. One recent study proposed that in light of the new understanding of L as a myeloid “stem cell” disease, the use of agents effective against acute myeloid leukemia might be a rational strategy [15]. Accordingly, institutional trials have reported the effectiveness of intermediate outpatient-dose cytarabine for LCH [15]. Still, this incomplete understanding of LCH pathogenesis has impeded clinical improvement [15]. The current standard of care for multisystem LCH, comprising empirically derived vinblastine chemotherapy and prednisone, cures fewer than 50% of patients, and optimal therapies for relapse and neurodegenerative disease remain uncertain [15].

CONCLUSION:

LCH is a mysterious hematological disease that can manifest a wide range of clinical symptoms associated with more common conditions, thus rendering a diagnosis challenging. Despite its initial description more than a century earlier, the pathogenesis of LCH is not yet fully understood. Furthermore, despite advances in understanding, the cell of origin of LCH remains unknown, leading to persistent questions regarding the “cytokine storm” that accompanies LCH. However, case reports in which LCH occurred in association with other histiocytic diseases (e.g., JXG and ECD) and advances in molecular studies suggest a myeloid origin for this disease. Unfortunately, the limited understanding of these factors has affected the clinical treatment of patients. Therefore, increased knowledge of this disease would improve both diagnostic and treatment methods.

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List of Abbreviations:

Langerhans cell histiocytosis	(LCH)
Birbeck granules	(BG)
Electron microscopy	(EM)
Juvenile xanthogranuloma	(JXG)
Erdheim–Chester disease	(ECD)
Pulmonary langerhans cell histiocytosis	(PLCH)
Merkel cell polyomavirus	(MCPyV)
Epstein–Barr virus	(EBV)
Bacillus Calmette-Guérin	(BCG)