

Langerhans Cell Histiocytosis: Clinical Presentation, Pathogenesis, and Treatment from the LCH Etiology Research Group at The Children's Hospital of Philadelphia

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Abstract: It is not uncommon for orthopedic surgeons to be called upon to evaluate a child with musculoskeletal manifestations of Langerhans cell histiocytosis (LCH). LCH is a disease that primarily affects bone but can be associated with a clinical spectrum that ranges from a solitary bone lesion with a favorable natural history to a multisystem, life-threatening disease process. Bone involvement with or without other associated sites is the most common manifestation of LCH and has been observed in 80–100% of cases. Despite the preference for bone, the disease may demonstrate extrasosseous manifestations as well. While uncommon, this may complicate the clinical picture, occurring most commonly in infants and children with multisystem disease. Although the described triad of diabetes insipidus (DI), exophthalmos, and eosinophilic granuloma does occur occasionally in children, multisystem disease may present in a variety of ways and may be life threatening. The microscopic examination is critical for the diagnosis. Immunohistochemistry using CD1a is now used routinely as a diagnostic tool. Although a positive CD1a immunohistochemical stain in the setting of appropriate histology is usually considered adequate for diagnosis, demonstrating Birbeck granules in the abnormally proliferating Langerhans cells using electron microscopy (EM) is the most specific diagnostic test. The etiology and pathogenesis of LCH has remained an enigma despite continuous research. Current theories suggest a role for environmental, infectious, immunologic, and genetic causes. A multidisciplinary research initiative has been underway at the Children's Hospital of Philadelphia (CHOP) division of orthopaedic surgery to better understand the etiology of this disorder. We have used cases and histological material from our pediatric database and tissue bank to investigate theories concerning the etiology of this disease. We postulate that the abnormal immune environment found in LCH patients may be associated with a musculoskeletal infection of the human herpes virus 6 (HHV-6). The search for an effective treatment has been unrewarding. Fortunately, most cases demonstrate a favorable natural history without treatment. The approaches to the treatment of LCH with extensive disease have been as variable as the presentation. However, further understanding the etiology will illicit more directed therapeutic approaches that will be more successful at establishing cure in LCH patients.

It may also allow earlier detection, prevention to those at risk, and the possibility for non-invasive diagnostic modalities.

Introduction

The disease Langerhans cell histiocytosis (LCH) is a disease that primarily affects bone but in rarer cases may also affect other organ systems or present as multisystemic disease [1–4]. Despite advances in understanding of the clinical picture, the pathogenesis of LCH is still unknown. A multidisciplinary team at the Children's Hospital of Philadelphia (CHOP) has been investigating the etiology of LCH and has convincing evidence that may help us better understand the etiology of LCH.

The use of different terminology to describe this condition has been as confusing as the search for its etiology. Terms that have been used over time to define LCH and associated conditions include histiocytosis X, eosinophilic granuloma, Letterer-Siwe disease, Hand-Schüller-Christian syndrome, Hashimoto-Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, Langerhans cell granulomatosis, Langerhans cell (eosinophilic) granulomatosis, type II histiocytosis, and non-lipid reticuloendotheliosis [5,6]. Recognizing that LCH has been named differently over time helps when reviewing the literature on this disease.

The annual incidence of LCH is reported at 5.4 million children per year [7]. Males are affected to a slightly greater degree than females [4,8]. It is predominantly a disease of childhood, with more than 50% of cases diagnosed between the ages of 1 and 15. There is a peak in the incidence between the ages of 1 and 4 [2]. In a study of 459 pediatric patients (less than 15 years of age), the youngest children were disproportionately affected. In this study of patients less than 15 years old, 53.8% of cases occurred before the age of 1, with another 18.1% occurring between the ages of 1 and 3 [7]. Although diagnosis often occurs in childhood, many cases of childhood onset progress into adult life [9].

There are three main clinical subtypes that are encompassed by the term LCH [5,8]. The first variant is a unifocal variant (single system, single site), and it has previously been referred to as eosinophilic granuloma. This subtype commonly involves bone (up to 80% of cases), lymph nodes, or lungs as a primary target [10]. Children with lo-

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calized disease tend to have bone involvement while adults have a greater propensity for lung involvement [11]. Based on a study of 459 pediatric patients (less than 15 years of age), this subtype has been documented to represent 33.3% of cases, with a median age at diagnosis in this group of 2.2 [7].

The second subtype is considered to be multifocal, and it has been referred to in the past as Hand-Schüller-Christian disease. This variant usually affects younger patients and involves several sites in one organ system (single system, multiple sites) [10]. The organ system involved varies from one patient to another. With cranial involvement, it often presents with skull lesions, diabetes insipidus (DI), and exophthalmos. Other bones, the oral cavity, skin, lymph nodes, brain, lungs, and liver represent other organ systems that may be affected in different patients [4]. Multiple foci of disease will be found in the particular organ system affected for a given patient. In a study of pediatric patients, this subtype has been reported to involve 15.1% of cases of children less than 15 years of age, with a median age at diagnosis of 3 [7]. This subtype is fatal in 15% of patients [11].

The third subtype, previously referred to as disseminated histiocytosis or Letterer-Siwe, affects multiple sites in multiple organ systems, and is most prevalent in young children and infants [10]. This variant is associated with the worst outcome [10]. Typical manifestations include multisystem involvement of bone and organs and may include persistent fevers, irritability, anorexia, failure to thrive, purpuric rash, superinfection, diarrhea, pancytopenia, and life-threatening sepsis [4]. Based on a study of pediatric patients, this subtype has been reported to include 51.6% of cases of children less than 15 years old. In this study, the mean age of diagnosis was 1.4, with most children diagnosed being under the age of 2 [7]. This form progresses rapidly and is usually fatal [11]. Despite its high prevalence in pediatric LCH patients, this variant represents less than 15% of all cases [4,7]. Thus, if diagnosed at a younger age, it is more likely that a child will have more serious disease with significant multisystem involvement. It is therefore apparent that young children suffer excess mortality rates from LCH, when compared to patients of other age groups.

Clinical Presentation

Bone involvement with or without other associated sites is the most common manifestation of LCH and has been observed in 80–100% of cases based on a review of the literature [2,12–15]. In one study, the average number of bones involved per patient was 1.4 [9]. In a study of adult and pediatric patients with bone involvement, 72% of 172 pediatric LCH patients had single bone involvement while 80% of the 91 adults with LCH (age 17–71) had single bone involvement [8]. To clarify the types of bone most frequently involved in LCH patients, researchers in a study of 503 osseous lesions identified lesions in the skull (27%), femur (13%), mandible/maxilla (11%), pelvis (10%), vertebral bodies (8%), ribs (8%), humerus (5%), and tibia (3%).

The bones of the hands and feet usually spared [4,8,9,11,12].

Clinically, patients present with fracture or pain at the site of the lesion, and when in the leg, limping. In a study of 263 adult and pediatric orthopaedic patients with a diagnosis of LCH in bone, 62% presented with complaints of localized pain and 48% complained of soft-tissue swelling that localized to the area of the bone lesion [8]. Because bone lesions are either symptomless or present as painful lumps that are often attributed by the patient to trauma, a diagnosis of LCH is often missed [12].

If examined with plain radiography, the appearance of the bone lesions can be variable and may depend on the stage of the process when the film is taken. When discovered, the destructive radiographic appearance of lesions may cause concern as they may mimic the radiographic appearance of primary bone infection or sarcoma, such as Ewing sarcoma and osteosarcoma [15] (Fig. 1). For this reason, LCH is sometimes referred to as the “great imitator.”

Early on, radiography often demonstrates single or multiple irregularly marginated lytic lesions ranging from 1 to 15 cm in diameter, often with a small soft-tissue mass, and with a wide zone of transition between lesion and adjacent bone [8,9,11,12,15]. Specifically, skull lesions, the most common location for LCH involvement, appear as lytic lesions with sharp borders and a “punched out” appearance. Lesions of long bone may include endosteal scalloping, cortical thinning, intracortical tunneling, and widening of the medullary cavity. In the spine, the lytic process can result in compression or collapse of the vertebral body, causing vertebral plana [2,14,16].

Many lesions share a common natural history detectable on radiography. Initially, aggressive lesions throughout the body may be associated with a permeative pattern of destruction with poorly defined margins [14]. These manifestations are often seen early in the progression of the lesion, when the bone cannot react fast enough to the destruction. Later, with progression of the disease, the lesion may become less active, and healing occurs. This gives a radiographic image signified by trabeculation of the lytic areas,

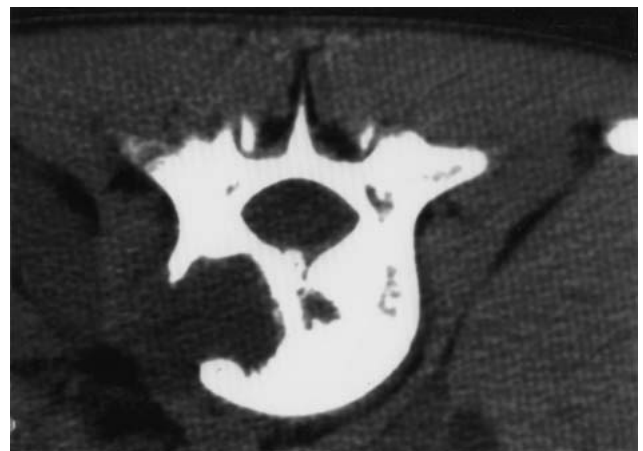


Fig. 1. CT image demonstrating a destructive LCH lesion of a lumbar vertebral body.

development of sclerosis of nonsclerotic lesions, and the loss of distinct margins [14]. Healed bone lesions may lead to permanent deformities of skull or long bones or to other deformities such as tooth loss [12,15].

Despite the preference for bone, LCH may demonstrate extrasosseous manifestations as well. This may complicate the clinical picture, occurring most commonly with multisystem disease. Although the described triad of DI, exophthalmos, and eosinophilic granuloma occurs in children, multisystem disease may present in a variety of ways across a wide clinical spectrum.

Skin involvement is common with LCH (up to 50% with multisystem disease may initially present with a rash), with the intertriginous zones and lumbosacral areas most commonly affected [12,17]. It is usually present in up to 80% of those with multisystem disease and 30% with less extensive multisystem disease [6]. It is reported as the only affected site in about 10% of cases [12]. It is often the first sign of multisystem LCH, and it becomes evident as scaly, erythematous, seborrhea-like brown to red papules [2,17], presenting in a fashion similar to contact dermatitis [6,12,17]. Patients with these skin lesions often present in the neonatal period and are characterized by eruption of nodular lesions that resemble those of healing chicken pox [17].

LCH lesions have an unexplained predilection for the hypothalamic/pituitary axis, usually occurring in the setting of systemic disease [18,19]. This can lead to disturbances in behavior, appetite, temperature regulation, or sleep patterns in the case of hypothalamic involvement [18]. Posterior pituitary involvement, resulting in DI is common in LCH patients, with incidence reports ranging between 5% and 50% [2,8,18,20]. This is the most prevalent endocrinopathy, and it may occur before, concurrent with, or after development of lesions in extracranial sites [2,4]. Polyuria or polydipsia, in excess of 6–8 liters of water intake daily, should be suggestive of a LCH diagnosis [12]. Such manifestations of LCH are significant because end organ damage resulting in DI may lead to lifelong dependence on desmopressin (DDAVP) hormone replacement [9].

Other endocrinopathies are less common but do occur in LCH patients. Growth retardation is uncommon at presentation but may occur as a late complication in a population of patients [4,12]. Eventual growth failure in these children is considered common [2]. Thyroid hormone deficiency may also occur as a result of anterior pituitary dysfunction [12]. Precocious or delayed puberty, amenorrhea, and hypocortisolism are other presentations representing anterior pituitary involvement [4,18].

Apart from lesions in the hypothalamus/pituitary region, the central nervous system (CNS) has also been reported to be involved in approximately 4% of patients with LCH [6,20]. Patients may develop cognitive impairment, emotional lability, changes in behavior, neurologic dysfunction, pyramidal signs, cerebellar symptoms, and cranial nerve palsy causing difficulties in speech and swallowing. This may eventually lead to marked cognitive and motor disabilities and can result in fatal CNS degeneration [19–21]. The most common manifestation is cerebellar symptoms, fol-

lowed by pyramidal signs and cranial nerve palsy [6,18,20]. Lesions may exert a mass effect, with symptoms depending on the size and site of the lesion [18].

Lymph nodes are sometimes enlarged in LCH patients (less than 10%), with those from the head and neck region preferentially affected [6,9,12,14]. Lymph node involvement results in partial preservation of lymph node architecture with distention of sinuses by typical Langerhans cell histiocytes [8].

Hepatic enlargement is very common in people with disseminated disease (up to one-third to one-half of children with disseminated disease have hepatomegaly) [6,12,14]. Overall, hepatosplenomegaly is seen in 4% of children and 1% of adults, based on a study of 263 LCH patients. Liver and spleen involvement usually signify a later stage of multisystemic disease or a manifestation of a more fulminant disease process [9]. Failure to control disease can lead to liver fibrosis and biliary cirrhosis [4,12].

Lung disease is frequent in multisystem disease, although the overall prevalence in LCH is estimated at less than 5%. It may cause respiratory distress with tachypnea, retraction, and persistent cough [12]. Primary lung involvement is usually found in adult smokers [6,21], and therefore lung disease is most common in adult LCH patients [12]. Although primary lung involvement in children is rare, its clinical manifestations are similar to those found in adults [6]. Children with uncontrolled LCH may develop chronic respiratory failure, presenting with cysts or bullae on radiographic examination [12].

Other common clinical manifestations of LCH include persistent otitis refractory to common treatment and hypertrophic gingivitis [4,12]. Oral manifestations may result in bleeding gums, early eruption, or even loss of teeth, and lesions simulating gingivitis or periodontal disease [14]. Although GI involvement is rare, the most common presenting sign is “failure to thrive” due to malabsorption [2,6].

Poor prognosis is signified by LCH involving bone and mucocutaneous tissue, cases involving both osseous and extrasosseous sites in multisystemic LCH, >3 bones involved, presence of mucous membrane LCH, presence of hepatosplenomegaly, and thrombocytopenia [8,9]. Poor prognostic factors have significant recurrence and mortality rates [4].

Diagnosis

The microscopic examination is critical for the diagnosis [22]. The tissues from LCH lesions contain an abnormal proliferation of histiocytic-like cells (Fig. 2, left) [2]. The lesions are locally proliferative and have been shown to demonstrate elevated proliferation rates ranging from 3% to 48%, with the largest indices found in the lymph nodes [5,6]. Characteristic pathologic morphology of tissue from children with LCH includes large cells with elongated, irregular nuclei, prominent nuclear grooves, folding, and indentation, moderate to abundant cytoplasm, and frequent mitotic figures [8,10]. Variable numbers of eosinophils are often present. The lesions are also characterized by osteo-

clast-like multinucleated giant histiocytes with bone destruction, necrosis, hemorrhage, and eosinophilic abscesses [6,8,13]. In one study, osteoclast-type giant cells were found in two-thirds of cases and tended to show great variability in number [8]. Also, indeterminate cells, interdigitating dendritic cells, macrophages, and T lymphocytes are often found in increased numbers in the lesions [4,8,9]. Granulomas may or not be seen, and fibrosis may be seen in later lesions [23].

On electron microscopy (EM), Langerhans cells are characterized by intracytoplasmic inclusions, rod-shaped or tennis racket-shaped profiles in sectioned material with a stippled line representing a transverse section through a paracrystalline net or lattice, called Birbeck granules (Fig. 3) [24,25]. Birbeck granules distinguish Langerhans cells from indeterminate cells at the ultrastructural level [4]. Therefore, the Birbeck granule is the only specific property of this phenotype, and demonstration of the Birbeck granule remains the gold standard of phenotype determination as well as diagnosis of LCH [5,6].

The CD1a immunohistochemical stain is a very helpful adjunct to the diagnosis, although a less specific marker of the pathogenic Langerhans cells (Fig. 2, right) [5,6]. A positive CD1a with the described histology in the right clinical setting is often considered adequate for diagnosis. Although S100 is not diagnostic, it is important in the evaluation of histiocytic disorders and identifies a family dendritic of cells that are part of cytological continuum [4–6].

Flow cytometry has demonstrated strong association between Langerhans cells and cell markers CD1, CD45, CD4, CD33, and HLA-DR [10]. Pathologic Langerhans cells have been shown to express CD14, which is unusual because normal Langerhans cells (LCs) poorly express this cellular marker [26]. This may reflect an immature stage of differentiation [26]. However, further experiments have proven that the cells are not “frozen” in this state, because they can

be induced *in vitro* to mature with an appropriate signal [26].

Pathogenesis

The hallmark of LCH is the abnormal proliferation of the LCs. Paul Langerhans first described the Langerhans cell in 1868 after making it visible by means of a gold chloride technique [27,28]. The Langerhans cell (LC) is considered to be a dendritic cell of the epidermis, making up 1–2% of epidermal cells, and is believed that it is derived from a multipotent bone marrow stem cell [4,6,10,25]. The LC is thought to be part of a spectrum of cells including macrophages, dendritic cells, including indeterminate cells or pre-LCs, LCs, interdigitating dendritic cells, and dermal dendrocytes [4]. It is a potent antigen-presenting cell that is essential for the integrity of the skin and of the immune system [17]. After antigen encounter, they migrate to regional lymph nodes where they present antigen to paracortical T cells [6].

The etiology and pathogenesis of LCH have remained an enigma despite continuous research. Current theories suggest a role for environmental, infectious, immunologic, and genetic causes; others believe that LCH is a neoplastic process. Flow cytometry sorting coupled with HUMARA polymerase chain reaction (PCR) confirmed that the CD1a⁺ Langerhans cells in LCH lesions are clonal [29–33]. However, a clonal proliferation does not necessarily mean that LCH is a neoplastic process [7,31,34–36]. The favorable natural history in most cases, the high probability of survival for patients older than 2 years of age [32], and the failure to detect aneuploidy or consistent karyotypic abnormalities [32] support the idea that LCH is not a neoplastic process or a malignancy. However, the proliferation of LCs may be a physiologically appropriate but clinically pathologic response [2].

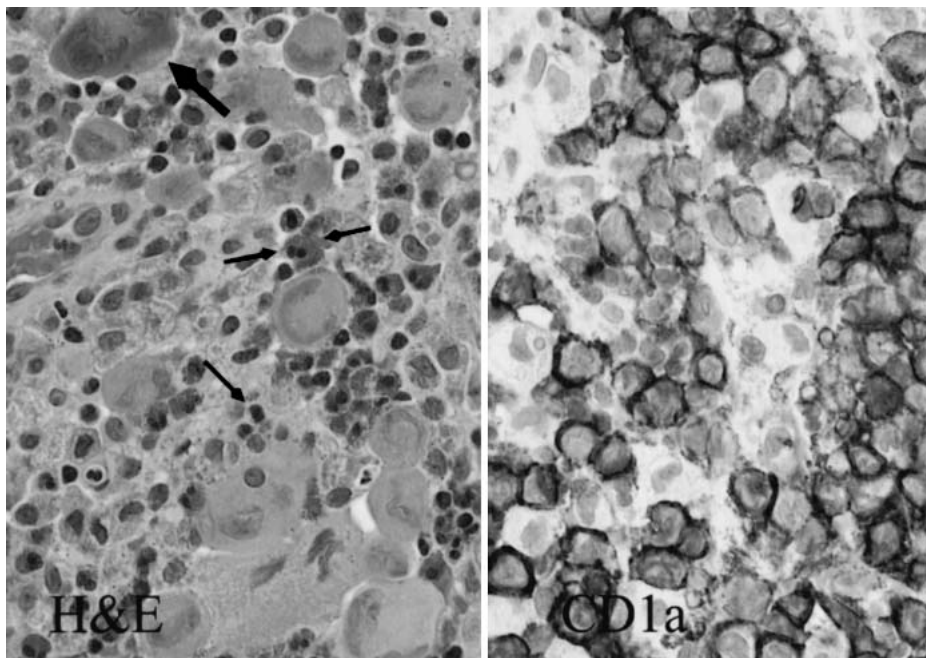


Fig. 2. Langerhans cell histiocytosis (LCH): hematoxylin and eosin (H&E, original magnification 60 \times) and LCH CD1a immunohistochemistry (original magnification 60 \times). H&E (left) demonstrates characteristic giant cells (large arrow), eosinophil infiltrate (eosinophil demonstrated between two small arrows), as well as lymphocytes (single small arrow). Positive CD1a immunohistochemistry (right) demonstrates characteristic membranous staining.

Increased numbers of LCs are present in lymph nodes of patients with a variety of viral diseases [37,38]. LCH may represent a reaction to a virus, but there is no convincing evidence at this point [32,39]. A comprehensive analysis of nine different viruses by in situ hybridization and PCR failed to prove an association among 56 specimens obtained from osseous lesions and lymph nodes [39]. However, 1 case in this study was reported to be positive for human herpes virus-6 (HHV-6) by PCR, and another five specimens demonstrated aberrant DNA bands of uncertain nature in analysis for HHV-6 [39].

A role for HHV-6 has been suggested by other studies. One report detected HHV-6 in 14 of 30 (47%) pediatric cases of LCH using PCR on paraffin-embedded samples [37]. The results had statistical significance when analyzed against the 63 control tissues composed of benign and malignant histiocytic/lymphocytic infiltrates of the skin [37]. In addition, an ultrastructural study of 50 pediatric cases [40] suggested that a viral agent might be responsible for LCH. They found numerous structures in pathologic LCs in LCH lesions on EM that suggested an increased local and/or systemic interferon production. They postulated that their data provides indirect evidence for a viral etiology [40].

In a recent investigation, the department of orthopaedics and the pathology department at the CHOP collaborated to examine tissue from our LCH database in efforts to clarify the role that HHV-6 has in the etiology of disease. We are in a unique position to study LCH because we have amassed a large number of patients with available tissue for analysis. During phase 1 of our investigation, in an analysis of 35 cases, we found HHV-6 in a high percentage of LCH lesional tissue by immunohistochemistry (IHC) and in-situ hybridization (ISH) that differed from control tissue from patients without LCH with statistical significance (in press). While some have looked for defects in the LCs, our data suggests that the abnormal immunological response may be

secondary to a viral infection of the lymphocytes. This may offer an explanation to the immune abnormalities found in LCH patients and also suggests that cells other than the pathologic LCs may play a key role in the pathogenesis of LCH.

We are continuing the research initiative to better clarify the role of HHV-6 in the etiology of LCH. Phase 2, underway, comprises further projects at the CHOP, including expanding the number of patients examined by IHC and ISH as well as quantitative molecular analysis. Future directions may also include prospective studies as well as serology analysis.

In fact there is other indirect evidence supporting a viral etiology. Aberrant or uncontrolled cytokine production is known to play a role in reactive histiocytic disorders [6,41,42]. Likewise, LCH patients may abnormally produce at least 10 different cytokines [3]. Most of these are of T-cell origin and may explain the recruitment of LCs, other inflammatory cells, over-expression of adhesion molecules, fibrosis, bone resorption, and necrosis. Interestingly, CD34⁺ hemopoietic precursor cells cultured in the presence of cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF) and TNF α , take on the complete LC phenotype including CD1a antigen and Birbeck granules [5]. This suggests that abnormal cytokines could potentially result in the abnormal proliferation of the LCs in LCH. The abnormal cytokine production may be due to a viral infection which may alter the cytokine expression of mononuclear cells [43–45] and interfere with dendritic cell functions. Thus, an inadequate response to a viral challenge may result in a local recruitment of immature LCs or their precursors, their abnormal homing, and their persistence in the absence of efficient maturation [26].

In addition, the chromosome instabilities described in the lymphocytes of LCH patients may be secondary to a viral insult [46,47]. One study analyzed phytohemagglutinin

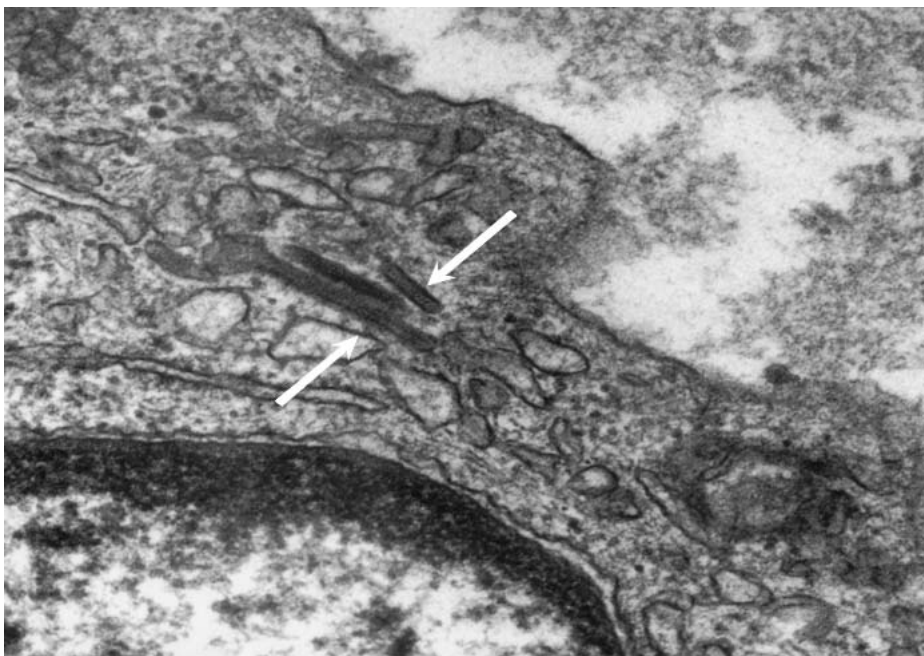


Fig. 3. EM demonstrating ultrastructural Birbeck granules (cluster between two arrows).

(PHA)-stimulated peripheral blood lymphocytes of LCH patients for cytogenetic abnormalities. Of the 16 patients analyzed, 11 demonstrated chromosomal abnormalities at a rate greater than the range of controls in the study. Abnormalities included chromosomal and chromatid breaks, polyploid cells, structural rearrangements, and cells with pulverization [47]. The authors suggested that the presence of different kinds of chromosomal alterations as well as a high variability in the number of chromosomal breaks is consistent with a hypothesis of a viral etiology for LCH. They suggest that chromosomal instability may be considered as a result of a reaction to an environmental agent, such as a virus [47]. This study is consistent with our findings and is in agreement with the theory that non-lesional cells may have a critical but yet undefined role in stimulating the abnormal proliferation of pathologic LCs. HHV-6 found in the lymphocytes of LCH patients may result in genetic changes that have a significant role in the pathogenesis of LCH.

Further evidence supports the theory that there is an underlying immune abnormality in LCH patients. It has been suggested that LCH patients have thymic abnormalities [48] as well as a suppressor cell deficiency [49]. LCH patients have also been shown to have thymic enlargement, as well as other abnormalities including dystrophic vascular appearing calcifications, nodular, and cystic changes [50]. These studies also suggest that lymphocytes may be important in the pathogenesis of LCH by contributing to the underlying immune dysfunction found in LCH patients.

Treatment

Many cases demonstrate a favorable natural history without treatment. One of the problems in choosing appropriate treatment lies in the fact that there is great ambivalence whether LCH is a neoplastic disorder or an immunodysregulatory disorder [51]. Because of this, there have been enormous gaps in the search to find appropriate treatment for patients [51].

For orthopaedic surgeons, after a biopsy is obtained, a conservative approach to the management of solitary bone lesions has been advocated for patients without significant pain or high potential for fracture [4]. Solitary bone lesions can be treated optimally with surgical curettage at the time of biopsy when the lesion is readily accessible [9,51]. Prognosis is excellent for those with restricted presentations [2]. Local radiation therapy or local radiation therapy after surgical excision has also been reported for the treatment of solitary bone lesions but carries significant long-term risk for growing children [9].

Although there is a general consensus that biopsy and local curettage are usually sufficient for the diagnosis and treatment of an isolated bone lesion, there is disagreement on how to treat those with acute refractory and progressive disease, chronic relapsing disease, and chronic and progressive multisystem disease with involvement of the lung, liver, and central nervous system [51].

Single-agent chemotherapy is the first line therapy for

these cases and is used to reduce morbidity because of the progressive nature of generalized LCH [2,9]. Various agents used include carboplatin, 2-chlorodeoxyadenosine, chlorambucil, cyclophosphamide, cytosine arabinoside, daunomycin, etoposide, mercaptopurine, methotrexate, mechlorethamine, procarbazine, vinblastine, vincristine, and vindesine [2,51]. They have shown to be effective, at least temporarily, in 50–60% of patients treated, but they often demonstrate high relapse rates [2,4]. In addition to the high relapse rates associated with these drugs, there are several other criticisms of the chemotherapeutic approaches used to treat LCH. Unfortunately, differentiating favorable response from favorable natural history is a problem when assessing the effectiveness of these drugs. Resistance to chemotherapy is also commonly encountered [51]. Also, some patients have developed malignancy after a diagnosis of LCH, such as the development of leukemia or solid tumors after treatment (<5%) for their LCH [52]. This brings to light some of the dangers that treatment approaches using chemotherapy may have in promoting a secondary malignancy [4,52].

Due the debate regarding the exact indications for chemotherapy as well as the unfortunate side effects associated with this treatment, several other treatment options have been used. A wide range of other therapies suggested includes topical steroids, intralesional injection of steroids, nonsteroidal anti-inflammatory agents, phototherapy, bone marrow allografting, hematopoietic stem cell transplantation, cyclosporin A, and prednisone. Unfortunately, the efficacy of these therapies has not been well documented [2,9,51].

Treatment is therefore directed by the clinical situation, and more aggressive approaches are used in patients with more extensive, multisystem involvement. However, there is only limited data of treatment modalities up to this point for multisystem disease. Having a better understanding of the etiology and pathogenesis of LCH will result in more directed and efficacious treatment regimens. Immunomodulatory approaches need to be evaluated more extensively, because their use may be favored over traditional chemotherapeutic approaches with confirmation of a viral etiology.

Conclusion

Children with LCH may present with clinical presentations involving a wide spectrum of osseous and extraosseous manifestations. HHV-6 has been implicated as a potential trigger, and a viral infection is now been considered as the underlying etiology. Based on our recent research, we postulate that HHV-6 plays an important role in the pathogenesis of this disease. We are in the process of conducting further studies to clarify the role of HHV-6. This will be done with further analysis from existing and future patient samples using IHC, more extensive ISH analysis, and molecular techniques. Further understanding the etiology and natural history of the disease will elicit ways for earlier detection, prevention, or detection of those at risk, and the

possibility of non-invasive diagnostic modalities. Also, it will lead to more directed therapeutic approaches that will have greater success in treating those with LCH.

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