

Langerhans Cell Histiocytosis of the Thymus in an Adult: A Case Report and Literature Review

xiao chuan zhang

zxcsdjn2025@126.com

The First Affiliated Hospital of Shandong First Medical University (Shandong Provincial Qianfoshan Hospital)

Case Report

Keywords: Thymic Langerhans cell histiocytosis, Clinical features, Pathological analysis, Case report

Posted Date: October 13th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10752661/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Objective

To investigate the clinicopathological features, genetic alterations, immunophenotype, and differential diagnosis of Langerhans cell histiocytosis (LCH).

Methods

A retrospective analysis was performed on a single case of adult thymic LCH, encompassing its clinicopathological characteristics, genetic testing, immunophenotype, and differential diagnosis, along with a review of the relevant literature.

Results

The patient was a 37-year-old male. Histopathological examination revealed characteristic morphological features of LCH. Immunohistochemically, the tumor cells were positive for Langerin, S-100, and CD1a, and partially positive for CD68.

Conclusion

The diagnosis of Langerhans cell histiocytosis was confirmed based on immunohistochemical findings (CD1a+, S-100+, Langerin+). In conjunction with a review of the literature, the possible pathogenic mechanisms and etiology of this disease are discussed to enhance understanding of this rare entity.

Introduction

The first confirmed case of Langerhans cell histiocytosis (LCH) was reported by Alfred Hand in 1893. Owing to shared histopathological features, Hand–Schüller–Christian disease, Letterer–Siwe disease, and eosinophilic granuloma were collectively classified as histiocytosis X in 1953, and subsequently renamed LCH in 1985. Histopathologically, LCH is defined by the proliferation of cells resembling Langerhans cells that are positive for both CD1a and Langerin [1]. The precise cellular origin of LCH remains unclear. The reported incidence of LCH is 3–5 cases per million population; the majority of patients are children under 3 years of age, whereas the incidence in adults is approximately 1–2 cases per million. In most instances, LCH presents as unifocal disease in older children and adults, commonly affecting bone (e.g., skull, femur, and pelvic bones), and less frequently involving lymph nodes, skin, or lung [2]. We herein report an adult patient with thymic LCH admitted to our institution. This article provides a detailed analysis of the etiology, pathogenesis, clinical manifestations, treatment, and prognosis of LCH, with the aim of enhancing clinical awareness of this disease.

Materials and Methods

1.1 General Information

Isolated thymic involvement by Langerhans cell histiocytosis is exceedingly rare in adults, having been reported primarily in patients with myasthenia gravis. We describe a case of unifocal LCH confined to the thymus, presenting as a solitary mass in a non-myasthenic adult. The patient was a 38-year-old male who presented with a one-day history of chest tightness. He reported intermittent chest tightness but denied dyspnea, chest pain, hemoptysis, cough, sputum production, choking sensation, fever, or dizziness. His past medical history was unremarkable; he had no chronic conditions such as hypertension, coronary artery disease, or diabetes mellitus. He had a 10-year history of smoking approximately 10 cigarettes per day and had quit prior to surgery. He also reported a 10-year history of alcohol consumption. There was no family history of neoplastic disease. Physical examination revealed a symmetric chest without deformity, clear breath sounds bilaterally, resonant percussion note, and no adventitious sounds. Contrast-enhanced chest CT demonstrated an anterior mediastinal cystic mass measuring approximately 2 × 2 cm. Admission laboratory investigations, including complete blood count, urinalysis, stool analysis, liver and renal function tests, serum electrolytes, cardiac enzymes, coagulation profile, and other hematological parameters, were all within normal limits. Electrocardiography was unremarkable. Abdominal ultrasonography (liver, gallbladder, pancreas, spleen, and kidneys) and bilateral lower-extremity venous Doppler ultrasound revealed no abnormalities, with patent venous flow. Following completion of preoperative evaluation with no contraindications to surgery, the patient underwent video-assisted thoracoscopic single-port mediastinal mass resection under general anesthesia, with complete intraoperative excision of the lesion. Intraoperative frozen section was suggestive of thymoma, type B3. Final pathology confirmed (mediastinal) thymic Langerhans cell histiocytosis, with a small amount of adipose tissue and thymic tissue. Immunohistochemical results showed CD1a(+), S100(+), Langerin(+), CK (epithelial+), P63 (epithelial+), CD68 (scattered+), CD3 (partial+), CD20 (partial+), and TdT (scattered+). This study strictly adheres to the Declaration of Helsinki

1.2 Methods

The specimens were fixed in 10% neutral-buffered formalin, routinely dehydrated, and embedded in paraffin. Sections of 4–5 µm thickness were cut, stained with hematoxylin and eosin (H&E), and examined under light microscopy. Immunohistochemical staining was performed using a fully automated Roche immunohistochemistry stainer. All antibodies were purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.

Results

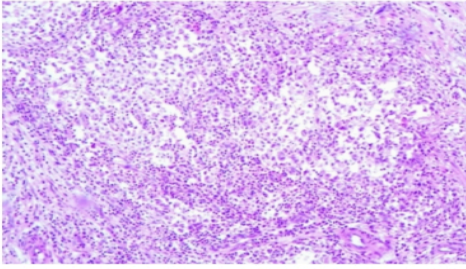
2.1 Histological Morphology

Mediastinal tissue was obtained for histological examination. Microscopically, medium-sized cells with markedly eosinophilic cytoplasm were diffusely distributed, with focal formation of epithelioid nest-like

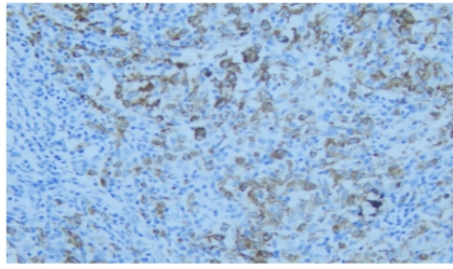
structures. The nuclei were oval, reniform, or coffee-bean shaped. The cells demonstrated abundant cytoplasm with indistinct cell borders and a pale eosinophilic appearance. Birbeck granules, the characteristic ultrastructural hallmark of Langerhans cells, were identified on electron microscopy.

2.2 Immunohistochemistry

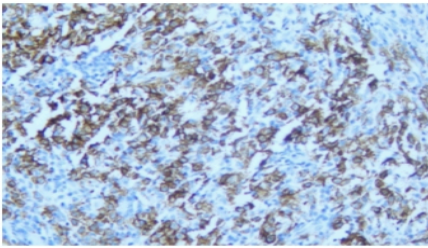
Immunohistochemically, the tumor cells showed positivity for Langerin, CD1a, and S-100, and partial positivity for CD68 and CD20.



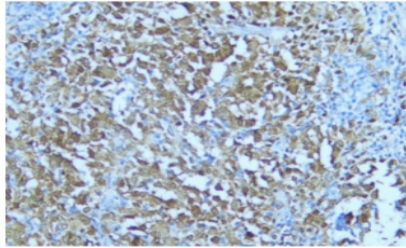
HE 100



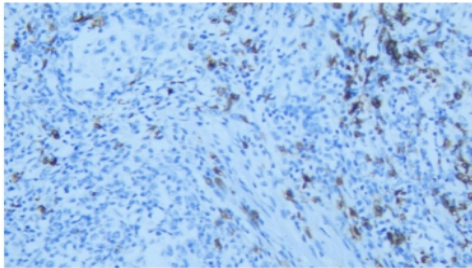
Langerin 200



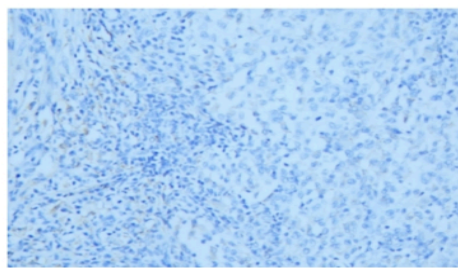
CD1a 200



S100 200



CD68 200



CD20 200

Discussion: Clinical Features of Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a rare clonal myeloid neoplasm characterized by the abnormal proliferation and infiltration of pathological Langerhans cells (or closely related dendritic cells). Epidemiological data demonstrate a marked age-dependent distribution, with an annual incidence of approximately 3–5 cases per million in children, making it the most common histiocytic disorder in children under 3 years of age and typically peaking between 1 and 3 years. In adults, the incidence is

considerably lower, at approximately 1–2 cases per million, and the clinical presentation, pattern of organ involvement, and treatment response frequently differ from those observed in pediatric patients. Gene expression profiling indicates that LCH cells more closely resemble immature myeloid dendritic cell precursors than epidermal Langerhans cells [1].

Clinical Classification

According to the extent and distribution of disease involvement, LCH is categorized as follows:

Single-system LCH (SS-LCH): Disease confined to one organ system.

Unifocal: A single lesion (most commonly in bone, e.g., skull or long bones).

Multifocal: Multiple lesions within the same organ system (e.g., multiple osteolytic lesions in a single bone or multiple skin rashes).

Special subtype: Lung as the sole involved organ (usually unrelated to smoking; more common in children; must be distinguished from a distinct adult subtype). **Multisystem LCH (MS-LCH):** Disease involving two or more organ systems. The key prognostic factor is the presence or absence of risk organ involvement (RO+ vs. RO–).

Molecular Pathogenesis

LCH is closely associated with aberrant activation of the MAPK signaling pathway (RAS-RAF-MEK-ERK). Approximately 75% of cases harbor mutually exclusive somatic mutations in this pathway, resulting in sustained ERK activation [3]. The most frequent alteration is the *BRAF*-V600E driver mutation, detected in 25%–65% of cases [4,5]. The identification of *BRAF*-V600E mutations in circulating CD11c⁺/CD14⁺ cells and in CD34⁺ hematopoietic progenitor cells from high-risk patients supports the concept that LCH is an inflammatory myeloid neoplasm driven by MAPK mutations in hematopoietic precursors [3].

LCH exhibits extensive infiltrative potential and can theoretically involve virtually any organ. Bone is the most commonly affected site (in approximately 80% of patients), particularly in children. It manifests as osteolytic lesions that may be accompanied by pain, swelling, or pathological fractures. The skull, femur, ribs, spine, and pelvis are frequently involved. Skin involvement is also common, especially in infants. Cutaneous manifestations are highly variable and include seborrheic dermatitis-like, eczema-like, papular, nodular, purpuric, or ulcerative lesions (particularly on the scalp, perineum, and trunk). Skin biopsy is an important diagnostic modality.

Central Nervous System Involvement

The classic manifestation of CNS involvement is infiltration of the hypothalamic-pituitary region (particularly the posterior pituitary), which often presents with diabetes insipidus as an initial and hallmark feature characterized by polydipsia and polyuria. This is among the most common CNS manifestations of LCH. Other presentations include involvement of the brain parenchyma

(neurodegenerative LCH), meninges, cerebellum, or cranial nerves, leading to corresponding neurological deficits such as ataxia, seizures, cognitive impairment, and visual or visual field defects. Magnetic resonance imaging is the primary modality for evaluating CNS involvement.

Other Potentially Involved Organs

Lymph nodes, ear (external otitis, mastoiditis), oral cavity/gingiva, gastrointestinal tract, thyroid, and thymus may also be affected.

Pulmonary LCH (PLCH)

PLCH is the most common and characteristic subtype in adult LCH patients. Pulmonary involvement in children usually occurs as part of multisystem disease or as single-system lung disease (unrelated to smoking). PLCH demonstrates an extremely strong association with cigarette smoking; more than 90% of PLCH patients have a smoking history [6]. Smoking is considered the principal environmental trigger for the development of PLCH in adults.

Treatment Cornerstone and Prognosis of PLCH

Smoking cessation is the most critical and effective intervention in the management of PLCH. Successful cessation often leads to disease stabilization or even remission (symptom improvement, radiographic regression, or stabilization of cystic changes), whereas continued smoking promotes disease progression. Unlike the typically clonal nature of childhood LCH or adult LCH at other sites, PLCH lesions are frequently polyclonal [6], suggesting that smoking may induce pulmonary inflammation and promote a reactive proliferation—possibly derived from polyclonal precursor cells—rather than a malignant clonal expansion of local Langerhans cells. Nevertheless, driver mutations (e.g., *BRAF* V600E) can still be detected in a subset of PLCH cases.

Pathological Diagnosis

When a lesional tissue biopsy is clinically obtainable, pathological examination remains the gold standard for confirming a diagnosis of LCH [7]. The core histopathological feature is the abnormal proliferation of Langerhans cells within involved tissue, accompanied by an infiltrate of lymphocytes, neutrophils, and eosinophils. The principal immunohistochemical diagnostic criteria include expression of Langerin (CD207), S-100 protein, and CD1a by the lesional cells. Birbeck granules may be identified in the cytoplasm on electron microscopy.

Treatment Principles

There is no universally standardized treatment regimen for adult LCH; management should be individualized according to disease subtype, extent of organ involvement, and disease activity. The core treatment strategies are outlined below.

1. Pulmonary LCH

More than 90% of adult PLCH cases are associated with smoking; complete and sustained smoking cessation is the only measure with the potential to induce remission or stabilization [6,10]. Intensive smoking cessation interventions (counseling, pharmacotherapy, etc.) should be implemented.

For progressive disease despite smoking cessation:

Systemic corticosteroids (e.g., prednisone 0.5–1 mg/kg/day, tapered gradually) were previously widely used, but evidence supporting their efficacy is limited; they are ineffective against cystic lesions and are primarily considered in patients with diffuse nodular or prominent inflammatory changes [10].

Cladribine (2-CdA) is currently the most effective pharmacologic option, particularly in patients with extrapulmonary involvement, and can induce relatively high response rates.

End-stage respiratory failure: Lung transplantation is the only curative option, with a 5-year survival rate of approximately 60–70%; however, relapse rates are as high as 20–30%, especially among those who do not quit smoking.

Role of radiotherapy: Its value in PLCH is limited, and it is not routinely recommended.

2. Multisystem LCH (MS-LCH) or Complex SS-LCH

This category includes involvement of two or more organ systems, or single-system involvement with "risk organ" involvement (RO+, e.g., hematopoietic system, liver, spleen) or CNS-risk sites (hypothalamic-pituitary region, brain parenchyma, cerebellum, or brainstem)

First-line systemic therapy: The conventional regimen is vinblastine (or vincristine) plus prednisone (VP), which constitutes the cornerstone of pediatric MS-LCH treatment. However, tolerability is poor in adults (significant neurotoxicity), and efficacy is lower than in children [11].

Alternative/optimized regimens: Cladribine (2-CdA) monotherapy or combination therapy (e.g., 2-CdA plus cytarabine [Ara-C]) has demonstrated superior efficacy to the VP regimen with manageable toxicity in adults and is gradually emerging as an important first-line option [13].

Cytarabine (Ara-C): Intermediate- or high-dose monotherapy or combination regimens (e.g., 2-CdA/Ara-C) are commonly employed in aggressive cases.

Aggressive or refractory disease: Intensive chemotherapy includes intermediate- or high-dose cytarabine-based regimens or anthracycline-containing regimens (e.g., doxorubicin), such as modified acute myeloid leukemia-type protocols [12]

Allogeneic hematopoietic stem cell transplantation (allo-HSCT): Indicated for patients who fail standard therapy, have very high-risk features (e.g., RO+ with poor response to chemotherapy), or experience relapse, provided they are young and have good performance status. Allo-HSCT offers potential for cure but carries substantial transplant-related risks [12].

3. Targeted Therapy: Focus on the MAPK Pathway

BRAF-V600E inhibitors (e.g., vemurafenib, dabrafenib) induce high and rapid response rates in patients harboring the *BRAF*-V600E mutation (present in approximately 50% of adult LCH cases) [13]. Major challenges include toxicity—cutaneous reactions (photosensitivity, rash, squamous cell carcinoma), fever, arthralgia, and elevated hepatic enzymes are common; close dermatologic monitoring and sun protection are required [13,14].

Second-generation BRAF inhibitors (e.g., PLX8394, belvarafenib): Designed to reduce paradoxical MAPK activation (thereby decreasing cutaneous toxicity) and may be effective against non-V600E *BRAF* alterations (e.g., fusions, insertions) [14].

MEK inhibitors (e.g., trametinib, cobimetinib): Indicated for patients with BRAF-wild-type disease who harbor *MAP2K1* (encoding MEK1) or other downstream MAPK pathway mutations (e.g., *ARAF*, non-V600E *BRAF*).

Combination targeted strategy (BRAF + MEK inhibitors; e.g., dabrafenib plus trametinib): This combination is already standard of care in *BRAF*-V600E melanoma. Preliminary data in LCH suggest it may improve efficacy (particularly in CNS-LCH), reduce cutaneous toxicity (by diminishing paradoxical activation), and potentially delay resistance; it is currently a promising combination regimen.

ERK inhibitors: Targeting the most downstream node of the MAPK pathway, these agents are being explored to overcome resistance to upstream (BRAF/MEK) inhibitors and may be combined with BRAF/MEK inhibitors to enhance efficacy [14].

Conclusion

In this group, the LCH case exhibited typical histomorphological features, with tumor cells immunopositive for S-100, P53, and CD1a. Studies have shown that the BRAF-V600E mutation rate is relatively low in Asian LCH patients [15]. Through the analysis of the histological morphology and immunophenotypic characteristics of this LCH case in our group, along with a review of the relevant literature, we have deepened our understanding of LCH, which aids in making an accurate diagnosis.

Declarations

Funding Declaration

No funding was received for this study

Conflict of Interest: The author declare no competing interests.

Author Contribution

References

1. Masayuki Kobayashi, Arinobu Tojo et.al Langerhans cell histiocytosis in adults: Advances in pathophysiology and treatment Revised,Cancer science Molecular Cancer (2017) 16:115.
2. Jaffe ES, Harris N. Vardiman. Tumours of haematopoietic and lymphoid tissues. World Health Organization Classification of Tumours, Pathology and Genetics. Lyon, France: World Health Organization; 2001. pp. 280–2.
3. Badalian-Very G, Vergilio J-A, Degar BA, MacConaill LE, Brandner B, Calicchio ML, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010;116:1919–23.
4. Héritier S, Hélias-Rodzewicz Z, Lapillonne H, et al. Circulating cellfree BRAFV600E as a biomarker in children with Langerhans cell histiocytosis. Br J Haematol. 2017;178(3):457–67.
5. Héritier S, Emile J-F, Barkaoui M-A, Thomas C, Fraitag S, Boudjemaa S, et al. BRAF Mutation Correlates With High-Risk Langerhans Cell Histiocytosis and Increased Resistance to First-Line Therapy. J Clin Oncol. 2016;34:3023–30.
6. Tazi A, de Margerie C, Naccache JM et al. The natural history of adult pulmonary Langerhans cell histiocytosis: a prospective multicentre study. *Orphanet J Rare Dis.* [
7. Huang HJ, Zhong DR. Clinicopathological and molecular features of Erdheim-Chester disease combined with Langerhans cell histiocytosis. Chinese Journal of Pathology, 2019, 48(3): 220–224.
8. Imafuku S, Shibata S, Tashiro A, Furue M. Cutaneous Langerhans cell histiocytosis in an elderly man success treated with narrowband ultraviolet B. Br J Dermatol. 2007;157:1277–9.
9. Atalar B, Miller RC, Dincbas F, et al. Adult langerhans cell histiocytosis of bones: a rare cancer network study. Acta Orthop Belg. 2010;76:663–8.
10. Vassallo R, Ryu JH, Schroeder DR, Decker PA, Limper AH. Clinical outcomes of pulmonary Langerhans’-cell histiocytosis in adults. N Engl J Med. 2002;346:484–90.
11. Tazi A, Lorillon G, Haroche J, et al. Vinblastine chemotherapy in adult patients with langerhans cell histiocytosis: a multicenter retrospective study. Orphanet J Rare Dis. 2017;12:95.
12. Ingram W, Desai SR, Gibbs JS, Mufti G. Reduced-intensity conditioned allogeneic haematopoietic transplantation in an adult with Langerhans’ cell histiocytosis and thrombocytopenia with absent radii. Bone Marrow Transpl. 2006;37:713–5.
13. Imashuku S, Kudo N, Kaneda S, et al. Treatment of patients with hypothalamic-pituitary lesions as adult-onset Langerhans cell histiocytosis. Int J Hematol. 2011;94(6):556–60.
14. Janku F, Amin HM, Yang D, Garrido-Laguna I, Trent JC, Kurzrock R. Response of histiocytoses to imatinib mesylate: fire to ashes. J Clin Oncol. 2010;28:e633–6.
15. Goyal G, Shah MV, Hook CC et al. Adult disseminated Lang $\ddot{u}$ erhans cell histiocytosis: incidence, racial disparities and longterm outcomes[J]. Br J Haematol, 2018(4). 579–81.