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RESEARCH ARTICLE

Diagnostic Heterogeneity in Langerhans Cell Histiocytosis: A Retrospective Series Emphasizing Morphologic Mimicry and Diagnostic Challenges

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Abstract

Introduction: Langerhans Cell Histiocytosis (LCH) is a rare disease of Langerhans-type dendritic cells. It is insidious in onset and shows a wide range of clinical manifestations, from solitary bone lesions to aggressive multisystem disease. The rarity of LCH, its multifaceted presentations, and histological similarities to other conditions frequently result in diagnostic delays. The aim of this study was to assess the clinical, radiological, histomorphological and immunohistochemical characteristics and to highlight diagnostic challenges faced along with factors influencing patient outcomes of LCH in our cohort. **Materials and Methods:** This is a retrospective case series where thirteen histopathologically confirmed cases of LCH were retrieved from patient medical records and histopathology reports from September 2018 to August 2025. Data were collected, tabulated, and analyzed by descriptive statistics using Microsoft Excel 2016. **Results:** In this study, LCH cases showed an age range of 11 months to 55 years with a median of 5 years. The male-to-female ratio was 3.3:1. Mean lesion size was 2.51cm. The majority of cases 6/13 (46.2%) were single-system unifocal. The most commonly involved site was bone 9/21 (42.9%). Lytic lesion on imaging was indicated in 100% of our cases with bone lesions. Immunohistochemistry (IHC) markers like Langerin, CD1a, S100, Fascin and CD68 were positive in 100% of the cases in which they were performed. The Ki-67 proliferation index varied across our cases, indicating variability in proliferative activity and showed median positivity of 20% (range of 10-70%). **Conclusion:** LCH can occur in diverse age groups and varied anatomic sites. An integrated diagnostic approach including clinicoradiological, histopathological and IHC correlation is required. A combination of IHC panel (Langerin, Fascin, CD1a, S100 supported by CD68 and a negative marker LCA) should be used rather than relying on a single marker, particularly in diagnostically challenging cases. Disease extent and risk-organ involvement were the main factors influencing clinical outcome, with multisystem diseases including risk organs having worse survival.

Keywords: Langerhans cell histiocytosis- clonal neoplasm- dendritic cell disorder- diagnostic challenges- histiocytic disease

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Introduction

Langerhans Cell Histiocytosis (LCH) is a rare clonal disorder involving pathological proliferation of dendritic cells derived from the myeloid lineage [1].

For children under 15 years of age, the incidence reported is 2.6 to 8.9 cases per million children per year. The incidence is even rarer and less precise for adults; the only available data is for disseminated disease, with 0.07 cases per million per year [2].

LCH has a wide and varied clinical spectrum. The most common symptom is skeletal involvement,

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which usually manifests as lytic bone lesions (80% cases). This is followed by cutaneous manifestations (20-40% cases) which can range from localized rashes to more widespread skin involvement. Patients may also exhibit oral symptoms like gingival hypertrophy and early tooth eruption, lymphadenopathy, thymic enlargement, chronic ear discharge, or soft-tissue masses, which are frequently located adjacent to bones. On the other hand, more aggressive disease biology is shown in multisystem disease with hematologic abnormalities, hepatosplenomegaly, or deranged liver function, which is linked to higher morbidity and death [3].

Diagnosing LCH is often challenging due to its varied clinical presentations and histomorphological mimicry which can closely resemble infections like tuberculosis or other histiocytic proliferations or neoplasms which may lead to delayed suspicion [4].

Histiocytoses classification was revised recently in 2016, and based on it, LCH has been classified as single-system LCH, lung LCH and multisystem LCH with or without risk- organ involvement (bone marrow, liver and spleen) [5]. While Sconocchia et al [6] have classified LCH as single-system disease [unifocal, multifocal, pulmonary, or Central Nervous System (CNS)] or multisystem disease, with or without risk-organ involvement.

The aim of this study was to assess the clinical, radiological, histomorphological and immunohistochemical characteristics and to highlight diagnostic challenges faced along with factors influencing patient outcomes of LCH in our cohort.

Materials and Methods

In this retrospective case series we analyzed thirteen histopathologically confirmed cases of LCH, including both single-system and multisystem LCH across all age groups. Patients without a histopathologically confirmed diagnosis were excluded from the study. The cases were retrieved from patient medical records and histopathology reports from September 2018 to August 2025. Data were collected, tabulated, and analyzed by descriptive statistics using Microsoft Excel 2016. Categorical variables were analyzed as frequency and proportions, while continuous variables were analyzed using median, range, and interquartile range due to non-normal distribution. Kaplan Meier survival graph was plotted using Software STATA version 16.1.

Results

In this study (Table S1 summarizes all 13 cases), LCH cases showed an age range of 11months to 55 years (median, 5 years; interquartile range, 20.9 years). The male-to-female ratio was 3.3:1. Unilateral and bilateral involvement was seen with equal frequency each accounting for 46.2% (6/13) of cases. Laterality was not applicable in 0.1% (1/13) cases. Among unilateral cases, left laterality predominated 83.3% (5/6) while right laterality was seen in 16.7% (1/6) of the unilateral cases. Single-system unifocal cases contributed to 46.2% (6/13). Single-system multifocal cases were 23.1% (3/13). Multisystem multifocal with and without risk-organ involvement cases each contributed to 15.4% (2/13). Mean size of the neoplasm in our study was 2.51cm. A total of 21 organ sites were involved across 13 cases, as some patients had multisystem LCH. Most commonly involved sites were bone 42.9% (9/21) followed by lymph nodes 23.9% (5/21), liver 9.5% (2/21), buccal mucosa, spleen, lung, scalp and orbital tissue each contributed to 4.8% (1/21).

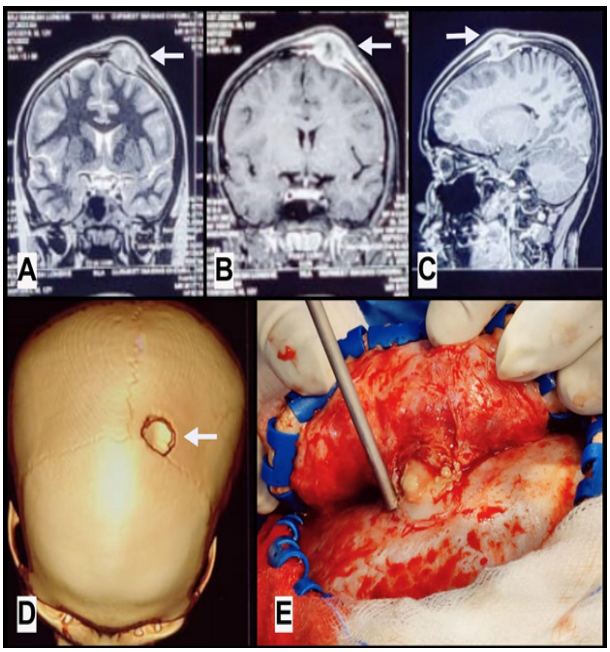


Figure 1. (A-D) Radiological images of case 5 indicating lytic lesion in parietal bone indicated by white arrows. (E) Intra-operative image of case 5 showing lesion in parietal bone.

In our study, all bone lesions 100% (10/10) demonstrated lytic lesions on imaging [Figure 1 (A-E) shows lytic bony lesions on radiology and intraoperative image of case 5 with parietal bone lesion), while lymph node involvement was uniformly identified as enlarged masses 100% (3/3). For immunohistochemistry (IHC) results please refer to Table 1.

Discussion

Earlier referred to as histiocytosis X, the name Langerhans cell histiocytosis is now favored as it better reflects the cellular origin of the condition, providing clarity on the nature of the neoplastic cells and eliminating the uncertainty suggested by letter 'X' [7].

The etiology and pathogenesis of LCH remain unclear; previous theories proposed that LCH is a reactive process. However, recent findings identifying BRAF and MAP2K1 mutations in most cases of LCH indicate that it is a clonal neoplasm arising from the uncontrolled proliferation of bone marrow-derived immature myeloid dendritic cells [1].

BRAFV600E is the most common mutation observed in LCH. The BRAF gene produces the BRAF protein,

Table 1. Immunohistochemistry Results by Case. Positive, Focal, Weak, and Negative Results are Indicated. Not done indicates tests not performed in that case.

Cases	Immunohistochemistry markers						
	S-100	Langerin	CD1a	Fascin	CD 68	Other markers	Ki67 (%)
1	Positive	Positive	Positive	Positive	Positive	LCA Negative	10
2	Positive	Positive	Positive	Positive	Positive	LCA Negative CK Negative CD3 Negative CD20 Negative Tdt Negative	50
3	Weak Positive	Positive	Positive	Positive	Positive	LCA Negative	15
4	Positive	Positive	Not done	Positive	Positive	LCA Negative	25
5	Positive	Positive	Positive	Positive	Positive	LCA Negative	10
6	Positive	Positive	Positive	Positive	Positive	LCA Negative	20
7	Positive	Positive	Positive	Positive	Positive	LCA Negative	70
8	Positive	Not done	Positive	Positive	Not done	LCA Negative	20
9	Positive	Focal Positive	Focal positive	Positive	Positive	LCA Negative	20
10	Positive	Positive	Positive	Positive	Not done	CD3 Negative CD20 Negative	20
11	Positive	Positive	Positive	Positive	Not done	LCA Negative	20
12	Positive	Not done	Positive	Positive	Not done	CK Negative CD3 Negative CD20 Negative CD30 Negative	15
13	Positive	Positive	Positive	Positive	Not done	LCA Negative CD3 Negative CD20 Negative Tdt Negative	30

which is a type of enzyme (serine/threonine kinase). This protein works as a part of the MAPK signaling pathway. The MAPK pathway plays a key role in controlling normal cell functions such as growth, division, differentiation, and survival. When BRAF is mutated, this pathway becomes abnormally activated, leading to uncontrolled cell proliferation seen in LCH. Among cases which lack BRAF V600E mutation, MEK gene mutation is common which activates MAP2K1 [6].

In addition to its molecular foundations, LCH has broad epidemiologic spectrum. Reisi et al [1] state that LCH primarily affects children aged 5 to 15 years, with a mean age of 3 years. Its presentation in neonates and adults is unusual, and individuals older than 50 years are exceptionally rare. The prevalence of LCH is higher in males [1]. In a study by Dhar et al [8], in a pediatric Indian population of 126 cases, the age at presentation was less than 5 years while the male: female ratio was 1.3: 1. Though direct comparison with study by Dhar et al [8] is limited due to age differences and organ involvement distribution, in our study, LCH cases showed an age range of 11 months to 55 years (median, 5 years; interquartile range, 20.9 years). The male-to-female ratio was 3.3:1, thus showing male preponderance in our study which is aligned with the literature.

The frequency of organ systems involved is bone (80%), skin (60%), liver, spleen, lymph nodes (33%), lungs (25%), orbit (25%) and maxillofacial (20%) [9]. The study by Dhar et al [8], revealed that 68% of the children presented with cutaneous lesions of which red scaly papules was the most common morphologic pattern (41.3%) of all the skin lesions. Skin involvement is more common in age groups less than 1 year, but overall, skin is the second most commonly involved organ in all age groups after bone [10]. In our study most commonly, involved sites were bone 42.9% (9/21) followed by lymph nodes 23.8% (5/21), liver 9.5% (2/21), buccal mucosa, spleen, lung, scalp and orbital tissue each contributed to 4.8% (1/21).

In the context of previously described clinical presentations, the most commonly associated symptoms in our study were fever 46.2% (6/13) and site-specific pain 46.2% (6/13) followed closely by palpable mass 44.4% (4/13) and lymphadenopathy 23.1% (3/13). Less common symptoms were weight loss 15.4% (2/13), followed by cough, breathlessness, teeth loss in the jaw lesion, head injury [each contributing to 7.7% (1/13)].

In our study, unilaterality and bilaterality were seen with equal frequency each accounting for 46.2% (6/13) of cases. Laterality was not applicable in 0.1% (1/13) cases. Among unilateral cases, left laterality predominated 83.3% (5/6) while right laterality was seen in 16.7%, (1/6), of the unilateral cases. In a 15-year series of nine orbital cases by Koka et al [11], five involved the right orbit and four

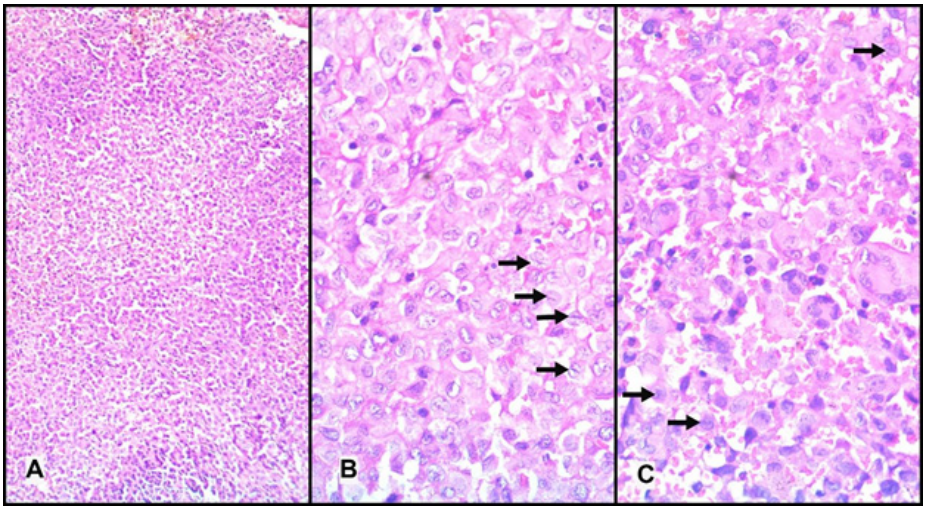


Figure 2. H&E images of case 7. (A) Low power view (10x). (B-C) High power view (40x) showing histiocytes with nuclear grooves (arrows) admixed with eosinophils and lymphocytes.

involved the left, with no bilateral cases documented. In our study, only one intraorbital case was present which reflected left laterality. According to a comprehensive review by Maia et al [12] bilateral lesions are significantly less common and more frequently occur in systemic disease as opposed to isolated skeletal LCH.

Depending on the organ and site affected, the mean size of lesions of LCH varies; nevertheless, imaging studies by Lim et al [13] showed that the mean size of lesions in the skull is approximately 2.26 cm, with a range of about 1.1 cm to 6.8 cm. While bone lesions in general can range from as tiny as 1 cm to the involvement of an entire long bone [14]. In our study, the mean lesion size of all thirteen cases was 2.51cm and the mean size of all lesions in skull was 2.26 cm (range of 1.5 to 3cm).

Within the recent 2016 classification framework of LCH, the predominant form of the disease is a single-system LCH of the bone, occurring in around 75-80% of cases, which may present as either unifocal or multifocal. The unifocal form is more common than the multifocal form [5]. In a study by Dhar et al [8], single-system cutaneous involvement alone was seen in 68% (86/126) of cases and 32% (40/126) had multisystem involvement. In our study, single-system unifocal cases accounted for 46.2% (6/13) while single-system multifocal cases were 23.1% (3/13). Multisystem multifocal with and without risk-organ involvement cases each contributed to 15.4% (2/13).

Histopathologically [Figure 2 (A- C)], the cells of LCH are large, round to oval, with a nuclear groove giving a coffee-bean appearance, and without the branching that characterizes inflammatory CD1a-positive dendritic cells. As LCH triggers the activation and recruitment of various immune cells, histopathological examination reveals an inflammatory pattern, featuring eosinophils, neutrophils, lymphocytes, and macrophages, interspersed with Langerhans cells. Eosinophilic lesions considered in the differentials in dermatologic lesions of head and neck region are epithelioid hemangioma, eosinophilic cellulitis (Wells syndrome), eosinophilic folliculitis,

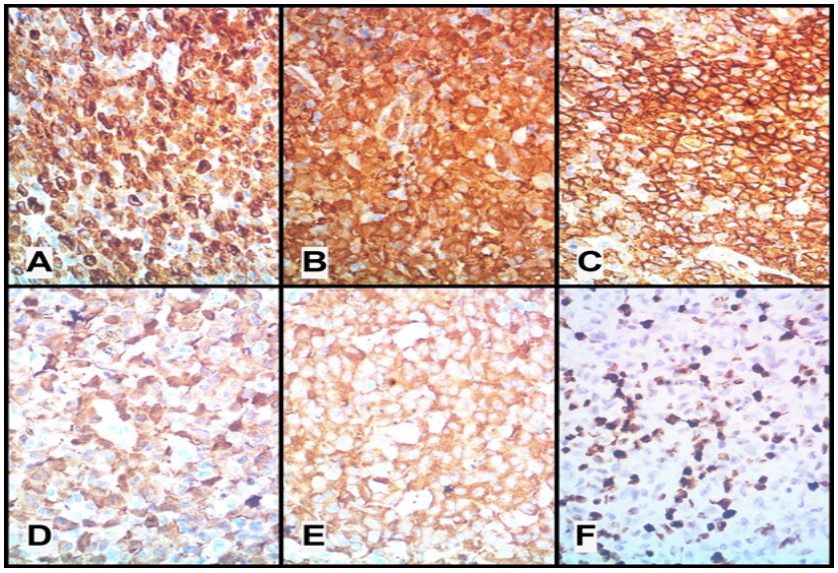


Figure 3. (A-F) High power view (40 x) of immunohistochemistry images of case 7 showing expression of (A) Langerin (cytoplasmic positivity), (B) Fascin (cytoplasmic positivity), (C) CD1a (membranous positivity), (D) S-100 (cytoplasmic and nuclear positivity), (E) CD68 (cytoplasmic positivity) and (F) Ki-67 (nuclear positivity).

eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), granuloma faciale [15]. In lungs, the differentials considered are eosinophilic pneumonia [16]. Allergies, infections, and certain malignancies can all have eosinophil-rich inflammatory infiltrates, but these lesions lack the pathognomonic Langerhans cell morphology and immunophenotype that LCH is known for, which includes CD1a, S100, and Langerin positive [17].

The histiocytic proliferation can mimic other histiocytic lesions like juvenile xanthogranuloma, malignant histiocytosis etc [17, 18]. Juvenile xanthogranuloma comprises foamy histiocytes and Touton giant cells and foamy histiocytes. It differs from LCH in that it is CD68 and Factor XIIIa positive but CD1a and Langerin negative [19].

Similar in appearance to LCH, indeterminate cell histiocytosis (ICH) is characterized by cells that are positive for CD1a and S100 but negative for Langerin. Thus, for diagnosis of LCH, CD1a as well as Langerin positivity is required [5].

Malignant histiocytosis is differentiated by overtly malignant cytological features like significant nuclear atypia, high mitotic rate, and typically complex karyotype, whereas traditional LCH shows intermediate-sized cells with nuclear grooves and limited atypia [5, 20].

Erdheim Chester Disease comprises foamy histiocytes with fibrosis. The cells are CD68 positive but CD1a negative while LCH shows both CD68 and CD1a positive. [21].

The diagnosis of LCH can be confirmed by identifying clonal neoplastic proliferation with expression of CD1a, Langerin, and S100 [Figure 3 (A-F) shows the immunohistochemistry images of case 7]. In limited diagnostic settings, in the presence of Langerin-positive cells of LCH, electron microscopy is no longer necessary for diagnosis. Nevertheless, the hallmark feature observed through electron microscopy remains the identification of Birbeck granules (pentalaminar cytoplasmic rod-shaped inclusions, a distinctive classic finding [2]. In our study (Table 1), although one case had weak staining, all thirteen cases were S100 positive (100%). Langerin was performed in 11 of the 13 cases, and all 11 (100%) showed positivity, with one case showing focal positivity. CD1a was done in twelve out of thirteen cases, and all twelve cases showed positivity (100%) with one case showing focal positivity. CD68 was tested in 8 of the 13 cases, and all tested positive (100%). Fascin showed positivity in all 13 cases (100%). LCA was negative in all eleven case where it was performed.

Despite these consistent IHC expressions, the diagnosis of LCH should not depend on a single marker expression in isolation. Rather, our results support the use of panel-based approach because IHC expression may be variable or focal or technically affected in limited or decalcified specimens. Based on our results, the practical diagnostic panel should include Langerin, Fascin, CD1a, and S100 as core diagnostic markers and CD68 to be used as supportive marker to confirm histiocytic lineage. LCA should be used to rule out lymphoid neoplasms, with additional markers used selectively based on morphologic and clinical differentials.

The median Ki-67 proliferation index in our study was 20%, with a range of 10% to 70%.

Certain instances with multifocal or multisystem disease showed higher Ki-67 indices, especially case 2 (50%) and case 7 (70%) respectively, the latter of which was a multisystem case with risk-organ involvement and a fatal outcome. However, a few single-system cases revealed overlapping indices, and some multisystem situations only had moderate Ki-67 values. Due to the small sample size and cohort variability, no consistent association between the Ki-67 index and disease category, risk-organ involvement, or outcome could be established overall.

In a study by Pinkus et al [22], neoplastic cells in all

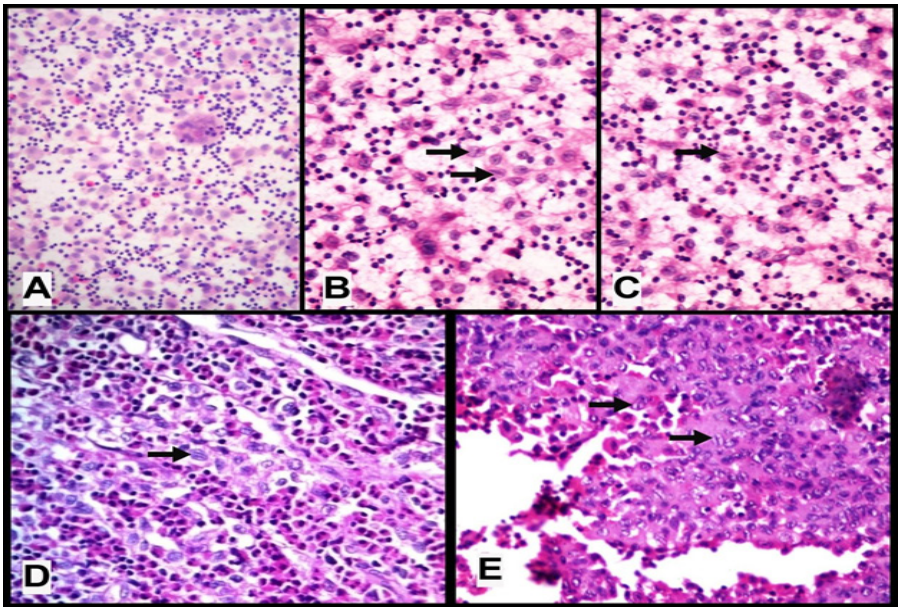


Figure 4. Images of case 8. (A) Hematoxylin and Eosin (H&E) stained FNAC image showing histiocytes admixed with eosinophils and occasional giant cell (10x). (B-C) FNAC & (D-E) H&E-stained biopsy images showing eosinophils and histiocytes with nuclear grooves (arrows) (40x).

34 LCH cases showed immunoreactivity for Fascin, CD1a and S100. Thus, all three markers were shown to be 100% positive in the neoplastic tissue. Azumi et al [23] studied 30 cases of LCH and showed S100 to be positive in 93% of cases (27/30).

Diagnostic imaging and histopathological analysis are used in conjunction to diagnose bone lesions of LCH. On imaging, a lytic lesion is the most typical radiologic indicator of bone involvement; it might have an expansile, moth-eaten, punched-out, or geographic pattern [24]. In this study, imaging revealed that all bone lesions 100% (7/7) demonstrated lytic lesions, while lymph node involvement was uniformly identified as enlarged masses 100% (2/2).

Given the potential for multifocal and multisystem disease, comprehensive imaging is essential at baseline. Whole-body fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (FDG)- PET/CT (vertex to toes) is recommended for disease mapping. High-Resolution Computerized Tomography (HRCT) used for suspected pulmonary involvement and Magnetic Resonance Imaging (MRI) with or without contrast for lesions involving the brain, spine, pituitary, or hypothalamus. Ultrasound (USG) of the abdomen is performed to assess liver and splenic involvement, with Endoscopic Retrograde Cholangiopancreatography (ERCP) reserved for cases showing abnormal liver function tests or biliary dilatation. In addition to imaging, tissue biopsy is required for definitive diagnosis, along with bone marrow examination in patients with abnormal complete blood counts, transthoracic echocardiography in pulmonary LCH, and endocrine evaluation when hypothalamic–pituitary involvement is suspected [25].

LCH presentations at unusual anatomical sites can mimic inflammatory and neoplastic diseases, creating diagnostic challenges. Three cases (Case 2, 4 and 8 of Table S1) of our study highlight such intricacies and challenges in diagnosing LCH.

Case 2 presented as a mediastinal mass with enlarged lymph nodes, which was initially sampled as a needle biopsy. The differential diagnosis on Hematoxylin and Eosin (H&E) included non-Hodgkin lymphoma, thymoma, and germ cell tumor. However, immunohistochemistry revealed S100, CD1a, Langerin, Fascin and CD68 positivity; LCA, CK, CD3, CD20, and Tdt were negative, and Ki-67 index of 50%, confirming the diagnosis of single-system multifocal LCH involving mediastinal lymph nodes.

Case 4 mimicked squamous cell carcinoma. Clinically, it presented with bilateral buccal mucosal lesions (2cm on the left and 0.8 cm on the right) along with right mandibular bone involvement. The initial biopsy suggested squamous cell carcinoma, where histiocytes were misinterpreted as malignant squamous cells. On the radical specimen, the final diagnosis was unveiled as LCH, with immunopositivity for S100, Langerin, Fascin, CD68 and a Ki-67 index of 25%. LCA was negative. In this instance, the location and morphology were fairly deceptive.

Case 8, (Figure 4) which was clinically suspected of tuberculosis, involved a 2.5 cm right cervical lymph node. FNAC suggested LCH, which was verified after a biopsy. Further radiological evaluation revealed multisystem multifocal involvement, including bilateral cervical lymphadenopathy, lungs, liver, spleen, and bone. Immunohistochemistry revealed positivity for S100, CD1a and Fascin. LCA was negative and the Ki67 index was 20%.

These instances demonstrate the diagnostic complexities of LCH, especially in small biopsies and situations when clinical and histomorphological features resemble more common conditions.

Thus, diagnostic challenges can arise due to limited size biopsies, inflammation related atypia, morphologic overlap with carcinomas or lymphomas or with clinico-pathological-radiological discordance if any. As this condition is rare, a validated predictive model cannot be suggested. However, a probable risk can always be flagged when strong suspicion exists, and timely immunohistochemistry evaluation can come to rescue.

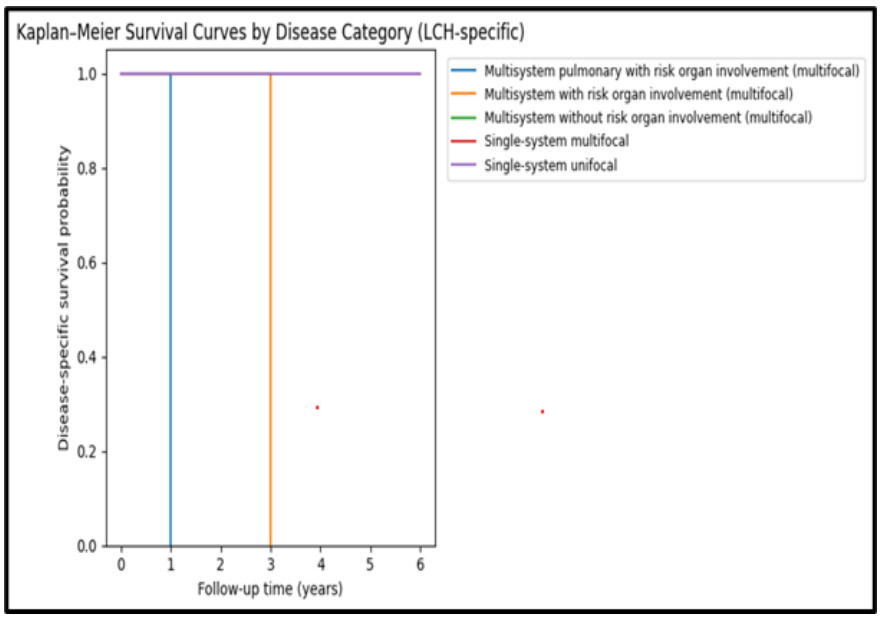
Diagnostic delay in our study was seen in cases mimicking regional common conditions like tuberculosis (case 8), squamous cell carcinoma (case 4) or lymphoma (case 2). Unisystem unifocal lytic bone lesions were diagnosed earlier as compared to multisystem disease, mediastinal mass, extranodal soft tissue lesions (Refer to Table S1 for time to diagnosis). Time to diagnosis in our study ranged from 0.5- 3 months. However, the delayed diagnosis seen in above mentioned scenarios did not result in disease progression, stage migration, treatment escalation, or adverse outcomes in any of our cases.

The treatment of LCH is tailored according to extent of the disease (single system or multisystem), focality (unifocal or multifocal), presence or absence of risk organ involvement (liver, spleen, bone marrow, CNS and the patient age (pediatric or adult).

For Unifocal Unisystem cases, if isolated bone involvement is present then complete excision of bone lesion (curettage) may be indicated if the lesion is small (less than 2 cm). However, aggressive excision of large lesions (>5 cm) is not recommended since it could cause persistent skeletal deformities by increasing the size of the bone defect and would lengthen the healing period. A biopsy and partial curettage are options for lesions 2–5 cm in diameter. To encourage healing, an intralesional injection of methylprednisolone or triamcinolone may be given, depending on the lesion's size and location. Bisphosphonates can also be given for isolated bone lesions. For isolated single lymph node involvement excision biopsy is the treatment of choice.

Unisystem multifocal cases are treated with individualised treatment which may range from observation for asymptomatic cases to local therapy like surgical excision or radiotherapy or systemic therapy.

For multisystem LCH, irrespective of mutation testing, for pediatric cases, vinblastine and prednisolone with or without 6 mercaptopurine is the standard treatment. In case of adults, irrespective of mutation testing, cytarabine or cladribine therapy is used. After the first six weeks, the response to treatment is a key predictor



Graph 1. Kaplan Meier Disease Survival Graph Stratified by Disease Category. This graph shows disease-related mortality was confined to multisystem disease with risk organ involvement, including pulmonary involvement. Single-system unifocal, Single-system multifocal and Multisystem without risk organ involvement (multifocal) categories demonstrated overlapping survival curves at 1.0 on the Y axis indicating excellent disease survival.

of the prognosis and progress of the disease. It has been demonstrated that maintaining treatment for at least a year lowers the chance of recurrence [25, 26].

For pediatric patients, the first line induction chemotherapy comprises injection vinblastine 6mg/m^2 intravenously weekly for six weeks and tablet prednisolone 40mg/m^2 orally for four weeks which is tapered over 2 weeks (V-P regime). For adults, injection cytarabine 100mg/m^2 intravenously daily for five days and is repeated monthly for 12 months or injection cladribine 5mg/m^2 intravenously daily for five days repeated monthly for 4- 6 cycles. For the continuation phase, regimen is chosen based on the response. For responders of the pediatric age group, if it is a low-risk patient, continuation of vinblastine and prednisolone (V-P regime) for 12 months is recommended. If it is a high-risk patient, 6-mercaptopurine is additionally given along with above mentioned V-P regime for continuation phase. For adults' continuation phase, cytarabine 100 mg/m^2 daily for 5 days every month for 6 to 12 months or cladribine 6 mg/m^2 intravenously for 5 days every 4 weeks for about 6 months [25, 27]. Treatment received by our cases is summarized in Table S1.

In pediatric patients, second line therapy is used for non-responders, if relapse is seen after 12 months, repeat the V-P regime and add 6 mercaptopurine or methotrexate. [27] Emile et al [5] recommend that BRAFV600E and MAP2K1 (MEK) mutations be tested in all patients who do not respond to first line therapy and in those in whom diagnosis is difficult [5]. The treatment includes targeted drugs like BRAF inhibitors (dabrafenib, vemurafenib) and the MEK inhibitor (trametinib). Dabrafenib is started at 50 mg orally twice daily, vemurafenib at 480 mg orally twice daily, and trametinib at 0.5–1 mg orally once daily [25].

In our study, second-line therapy was required in case 7. This pediatric patient had multisystem disease with risk organ involvement (treatment details are shown in Table S1). The patient initially responded to first-line therapy and remained in remission for subsequent one year. Disease progression was later noted, following which second-line treatment with the V-P regimen and methotrexate was started and continued for one year. Despite this, the patient showed further progression and succumbed to the disease at the end of three years of follow-up.

Along with treatment protocols, careful attention to treatment related toxicities is also essential.

The targeted therapies like BRAF and MEK inhibitor therapies are associated with specific toxicities, patients on BRAF inhibitors need regular dermatological examination and ECG monitoring (to rule out skin toxicities and cardiomyopathy, while those receiving MEK inhibitors require additional retinal examinations along with skin and heart surveillance [25].

In our study, the only treatment-related toxicity observed was transient neutropenia in two cases (case 7 and 8) who received systemic chemotherapy, which resolved with supportive care. None of our cases were treated with BRAF or MEK inhibitors, therefore targeted therapy related toxicities were not seen in our study.

Children with bone lesions in the orbit, temporal bone, sphenoid, mastoid or clivus are at risk for developing diabetes insipidus (DI) and/or neurodegenerative CNS LCH. The incidence of DI is 12% in the LCH-III research, which employed vinblastine/prednisone for one year. Following vinblastine/prednisone treatment, patients may benefit from cytarabine or clofarabine if their condition is refractory or recurrent [28].

For multisystem CNS involvement the recommended treatment in pediatric patients is vinblastine with prednisolone or cytarabine monotherapy. If there is LCH associated with abnormal CNS imaging or neurodegeneration a therapy of cytarabine with or

without intravenous immunoglobulin. BRAF inhibitors (vemurafenib, dabrafenib) or MAPK inhibitors (trametinib) are used if CNS penetration is seen [25]. Our case 11 (Multisystem-CNS without risk organ involvement, multifocal) was treated with systemic chemotherapy. Details of this case are provided in Table S1.

The follow- up protocol for our cases was response assessment at 3 months and 6 months by clinical examination and imaging (CT scan/MRI) every 6 months. Our follow-up period ranged from 1 year to 6 years.

Two of our multisystem cases (case 7 and 8) succumbed after three and one year of diagnosis respectively due to disease progression [15.4% (2/13)] while case 10 succumbed five years after diagnosis due to cause unrelated to LCH (Covid-19). All remaining patients are alive till date and were in clinical and radiological remission at the time of last follow-up 76.9% (10 /13).

The Kaplan-Meier survival graph (Graph 1) in our study shows that the main factors influencing the outcome of LCH are the extent of the disease and the involvement of risk organs. Single-system disease and multisystem disease without risk organ involvement showed uniformly favorable disease-specific survival. In contrast, multisystem disease with risk organ involvement, particularly pulmonary involvement, was associated with disease-related mortality. (The case which died due to cause unrelated to LCH was excluded from the Kaplan Meier survival graph).

In a study by Dhar et al [8], over the course of three to seven years, 56.9% of children experienced complete remission, whereas 31.8% of children died from complications and 8.1% of children were lost to follow-up.

Limitations of the study

A limitation of this study is the lack of molecular testing for BRAF V600E and MAP2K1 mutations. Molecular analysis could not be performed due to financial constraints and also restricted availability of archival tissue in some cases due to retrospective nature of this study. Consequently, mutation-specific prognostic stratification and assessment of eligibility for targeted therapies, was not evaluated in this study. However, a thorough histomorphologic evaluation supported with immunohistochemistry panel were used to diagnose every case in the current study. To better understand genotype-phenotype relationships and therapeutic implications in this population, future prospective studies using molecular testing are necessary.

In conclusion, this study demonstrates the broad clinicopathologic spectrum of LCH in varied anatomic locations and varied age groups (from infancy to adulthood) with predominant pediatric presentation. The most frequent presentation was skeletal involvement, which consistently showed up on imaging as lytic lesions. Predictors of delayed diagnosis in our study were non-skeletal manifestations, deep-seated lesions, and overlap with infectious or malignant differentials like tuberculosis or neoplasms (lymphoma and squamous cell carcinoma) respectively. Thus, a targeted immunohistochemical panel and meticulous clinicoradiologic correlation is recommended. The overall IHC profile highlighted the necessity of a combination panel (Langerin, Fascin, CD1a, S100, supported by CD68 to confirm histiocytic lineage and a negative LCA to rule out lymphoma) rather than relying on a single marker. Even though certain multisystem and risk-organ-involved cases had higher Ki-67 indices, no reliable predictive correlation could be found. Survival analysis revealed that disease extent and risk-organ involvement were the most important predictors of outcome, with poor survival limited to multisystem disease with risk-organ involvement.

Thus, this study adds significant insight from Indian tertiary-care settings and emphasizes the significance of early detection of atypical presentations to enable prompt and appropriate management.

Declarations

Clinical trial registration

Not applicable

Conflicts of interest/Competing interests

Authors declare that they have no conflicts of interest.

Availability of data and material

The data sets used and/or analyzed during the current study are available from the corresponding authors per reasonable request.

Code availability

The custom code was used.

Authors' contributions

Authors 1 and 2 contributed to the conception, design, and final drafting of the manuscript.

Author 2 contributed to the primary drafting of the manuscript along with data analysis. Authors 3, 4, and 5 collected the data, reviewed the manuscript for important intellectual content, and supervised the study. All authors approved the final version for submission and also accept responsibility for all aspects of the work.

Ethics approval

Not applicable

Consent to participate

Written informed consent was obtained from all participants, and the trial was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from all participants, and the trial was conducted in accordance with the Declaration of Helsinki.

Originality Declaration for Figures

All figures included in this manuscript are original and have been created by the authors specifically for the purposes of this study. No previously published or copyrighted images have been used. The authors

confirm that all graphical elements, illustrations, and visual materials were generated from the data obtained in the course of this research or designed uniquely for this manuscript.

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None.

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