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Case Report

Recurrent Multifocal Langerhans Cell Histiocytosis With Orbital Manifestation

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Abstract

Background: Langerhans Cell Histiocytosis (LCH) is a rare disease and is more common in children than adults. The incidence is estimated to be approximately 5–10 cases per million children annually. LCH has a wide range of clinical manifestations with rare orbital involvement.

Case Presentation: Here, we report a six year-old-girl with recurrent multifocal LCH a year after chemotherapy accompanied by orbital manifestation, present as proptosis of left eye, lagophthalmos, and left superior palpebral abscess with fistula. She had a history of occipital brain LCH with bone involvement, which was surgically removed four years before admission. Ocular examination showed limitations on ocular motility, proptosis, inferonasal displacement of the globe, lagophthalmos, eyelid edema, and hyperemia. In contrast, Head Magnetic Resonance Imaging (MRI) revealed a mass in the left superior orbit and the right occipital condyle. Histopathological examination reveals pathological Langerhans cells with eosinophils and giant cells. The patient was treated with symptomatic drugs while chemotherapy and eyelid reconstruction were planned.

Conclusion: LCH is a disorder with highly diverse clinical manifestations. Orbital involvement is one of the uncommon presentations of LCH and necessitates a comprehensive clinical assessment. Early and accurate diagnosis is crucial. Although LCH can lead to serious complications if not promptly treated, recurrence of the disease is relatively rare. Nevertheless, long-term follow-up is recommended to ensure early detection of any potential recurrence and to maintain optimal patient outcomes.

Keywords:

Langerhans cell histiocytosis
Ocular proptosis
Orbital tumor
Recurrence

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1. INTRODUCTION

Langerhans Cell Histiocytosis (LCH) is a rare disease characterized by pathological proliferation of cells from monocyte-macrophage lineage and dendritic cells [1]. LCH is more prevalent in children and is estimated to be approximately 5–10 (five to ten) cases per million children per year [2, 3]. LCH can affect multiple organs [4]. Ophthalmologic manifestations can occur in anterior and posterior orbital locations [1, 5]. Definitive diagnosis requires histopathological examination.[1] Treatment for LCH is based on the extent of the organ [2]. Chemotherapy is a viable option for multifocal disease, recurrences, and orbital lesions with dural involvement [1, 6]. This case report aims to review a patient's clinical presentation with orbital LCH.

2. CASE PRESENTATION:

A 6-year-old girl had a history of occipital brain tumor with bone involvement, which was surgically removed and replaced with an acrylic skull implant four years before admission to the oncology clinic at the hospital. The diagnosis then was Langerhans cell histiocytosis based on anatomical pathological findings. She was then referred to the hospital for further investigation. One year later, she underwent the removal of an acrylic skull implant because of infection and then received 20 (twenty) cycles of chemotherapies with vincristine, prednisone, methotrexate, and cyclophosphamide. During post-chemotherapy follow-up, she complained of a protruding left eye persisting for months before admission to the eye oncology clinic, which was accompanied by watery eyes, a red-swollen eyelid, and itchiness. Pus then appeared on the upper lid of the left eye and was diagnosed with a left superior palpebral abscess with a fistula. Therefore, she underwent orbital exploration and drainage incision. However, she still complained of a protruding left eye.

An ocular examination revealed a visual acuity (VA) of 5/5 (five per five) and normal eye palpation. The ocular motility of the left eye was limited to superolateral, lateral, and inferolateral movements without pain. Examination of the left eye's anterior segment showed proptosis, inferonasal displacement of the globe, lagophthalmos, eyelid edema, hyperemia, tarsorrhaphy on the eyelids, conjunctival hyperemia, and a positive corneal fluorescein test (**Figure 1 (a-d)**). A head Magnetic Resonance Imaging (MRI) with contrast revealed a mass in the left superior orbit and right occipital condyle, accompanied by hyperostosis of the left sphenoid wing extending to the calvaria of the left frontal bone, causing proptosis of the left eye and expansion into the danger space and right retropharyngeal space (**Figure 2**). The diagnosis was multiple extra-axial tumors in the retrobulbar, left frontal, and occipital regions, suspected recurrent Langerhans cell histiocytosis, with left eye lagophthalmos complicated by exposure keratopathy and palpebral edema. The patient underwent a craniotomy for tumor excision with unroofing of the left orbital roof, lateral orbitotomy of the left eye, and osteoplasty. Intraoperative findings revealed a granulation mass in the temporal basal area extending to the orbital roof, partially infiltrating the bone. Anatomical pathology showed a tumor tissue slice consisting of cells with round, pleomorphic nuclei, some vesicular, with moderate to extensive cytoplasm, mitoses 6/10 (six per ten) high-power field (HPF), and a dense distribution of eosinophil cells, along with a few inflammatory lymphocyte cells and areas of bleeding (**Figure 3 (a-d)**). Post-surgery, the patient was treated with topical antibiotics for exposure keratopathy. The patient is currently planning eyelid reconstruction for lagophthalmos and undergoing chemotherapy.

3. LITERATURE REVIEW

3.1. Definition

Histiocytic disorders are uncommon conditions marked by the accumulation of macrophages, dendritic cells, or monocyte-derived cells in different tissues throughout the body [7]. It can be divided into three categories: Langerhans cell (LC), non-LC related, and malignant histiocytosis [7, 8]. The WHO classification of hematopoietic and lymphoid tumors groups disorders involving these cells into three main categories: (1) *Dendritic cell disorders*, which include Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), juvenile xanthogranuloma, and solitary histiocytomas with a dendritic cell phenotype; (2) *Macrophage-related disorders*, such as Rosai-Dorfman disease and solitary histiocytomas with a macrophage phenotype; (3) *Malignant histiocytic disorders*, which encompass monocyte-derived leukemias, extramedullary monocytic tumors, and dendritic cell-associated histiocytic sarcomas [7]. All of these conditions involve a localized overgrowth of histiocytes. Still, they are distinguished by differences in their cellular morphology, histochemical and immunohistochemical staining characteristics, and ultrastructural features observed under electron microscopy [7].

Langerhans Cell Histiocytosis (LCH), otherwise known as histiocytosis X, encompasses several clinical variants, including Hand–Schüller–Christian disease, which presents as LCH with a classic triad of exophthalmos, lytic bone

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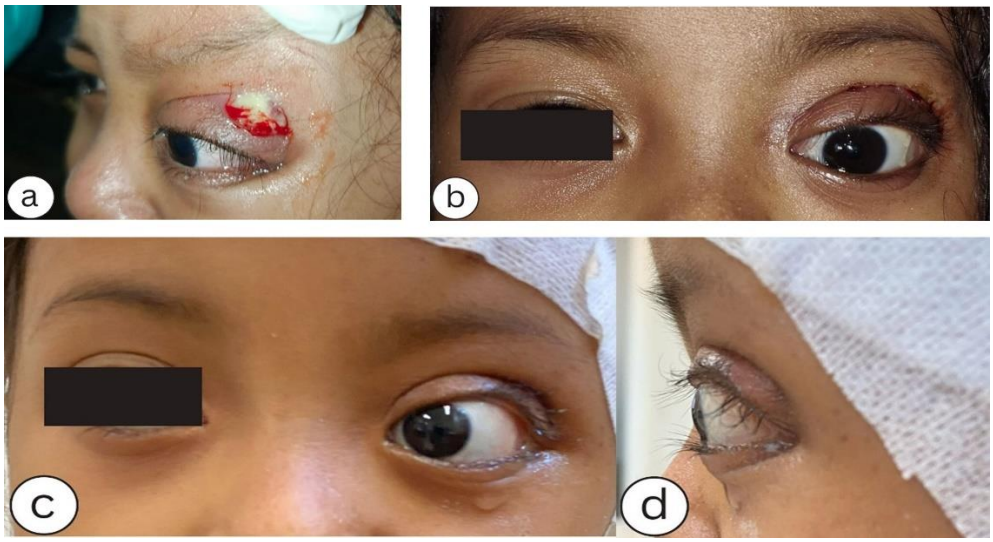

Figure 1. Clinical presentation of the patient before undergoing craniotomy excision of the tumor: **(a)** palpebral abscess with fistula of the left eye, **(b-d)** proptosis and upper lid retraction of the left eye after craniotomy excision of the tumor.

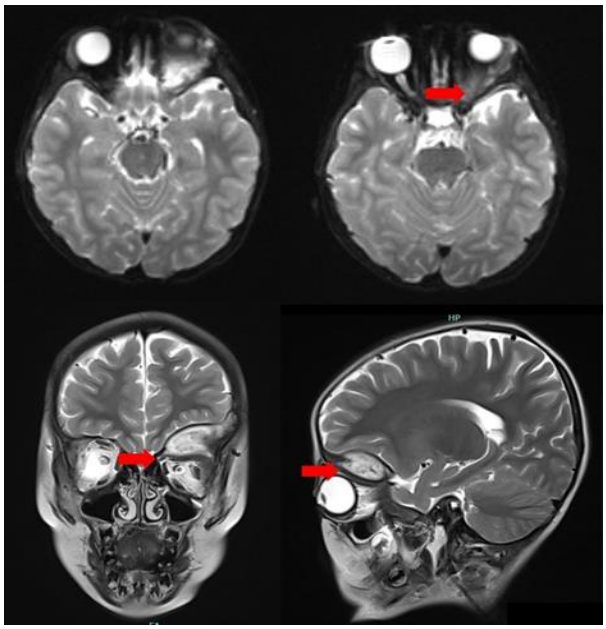

Figure 2. Contrast head Magnetic Resonance Imaging revealed a mass in the left superior orbit accompanied by hyperostosis of the left sphenoid wing extending to the calvaria of the left frontal bone, as shown by the red arrows.

lesions, and diabetes insipidus; Letterer-Siwe disease, characterized by acute and fulminant disseminated LCH; and eosinophilic granuloma, which represents a more indolent, chronic form of LCH marked by granulomatous lesions in bone or other organs [7-11]. It is characterized by the abnormal proliferation of histiocytes—specialized dendritic cells of the immune system responsible for presenting antigens to T-lymphocytes [7-11].

3.2. Epidemiology

LCH is a rare condition, occurring in approximately 0.2 to 2.0 cases per 100,000 children under the age of 15

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worldwide [11]. Although it can develop at any age, it most frequently occurs in children, particularly between the ages of 5 and 10, and commonly affects the orbit in about 23 – 37.5% of cases [11].

The 63 articles featured 99 patients from various demographics (Table 1). The average age of the patients in the case reports was 13.75 years, with a median of 8 years and a range of 4.5 months to 61 years old. The sex distribution was 59 males (60%) and 40 females (40%). The average age of male patients was 14.6 years old, with a median of 9 years old. The average age of female patients was 12.5 years old, with a median of 6.5 years old. The youngest male patient was 4.5 months old [12], and the oldest male patient was 61 years old [13]. The youngest female patient was 8 months old [14], and the oldest female patient was 57 years old [15].

3.3. Pathophysiology

The pathogenesis and biological nature of Langerhans Cell Histiocytosis (LCH) remain subjects of ongoing debate and investigation [7, 11, 16]. Unlike normal Langerhans cells, the histiocytic cells in LCH lack the characteristic dendritic morphology [7, 17]. Current evidence suggests that the actual cell of origin is not the epidermal Langerhans cell but rather a myeloid-derived dendritic precursor that expresses key markers such as CD1a and CD207 [7, 17].

The underlying nature of LCH continues to be debated, particularly regarding whether it represents a reactive immunologic disorder or a clonal neoplastic disease [7, 10, 11, 16]. Support for the reactive hypothesis includes elevated cytokine levels in affected individuals, suggesting an exaggerated immune response that may contribute to disease pathogenesis [7, 10, 16]. Immune dysregulation in LCH may be triggered by various factors, including viral infections, genetic predisposition, lymphoma, leukemia, or myelodysplastic syndromes [7, 10, 16]. Transient immunologic triggers such as viral infections are often associated with localized (unifocal) disease, whereas persistent immunodeficiency may promote multisystem or disseminated involvement [7, 10, 16].

Conversely, the neoplastic theory is supported by identifying multiple genetic alterations in LCH cells. These include loss of heterozygosity, chromosomal abnormalities, and activating mutations in oncogenes—most notably the BRAF V600E mutation, which is detected in approximately 50–60% of cases. These molecular changes support the concept of LCH as a clonal disorder and provide a plausible explanation for the uncontrolled proliferation of pathologic Langerhans cells [16].

3.4. Clinical presentation

LCH exhibits a highly variable clinical presentation and progression [11, 17]. It can affect multiple organs and systems, with the lungs and bones being the most commonly involved areas [11]. The LCH Study Group classifies the disease into two main types: single-system LCH (S-LCH) and multisystem LCH (MS-LCH) [16]. S-LCH is further categorized into unifocal, affecting a single site such as bone, skin, or lymph nodes, and multifocal, involving multiple sites within the same system, like bones and lymph nodes. MS-LCH, on the other hand, involves two or more organ systems and is divided into low-risk forms—where critical organs like the liver, lungs, spleen, and bone marrow are not affected—and high-risk forms, in which one or more of these vital organs are involved [16].

Orbital LCH is an uncommon condition that poses diagnostic challenges due to its overlapping radiological characteristics [11, 18]. It most often represents a unifocal disease [16]. The most frequent clinical signs of orbital LCH are eyelid swelling and exophthalmos [11, 18]. It also commonly appears as a solitary bone lesion accompanied by a soft tissue mass, usually located in the superior or superior-temporal region of the orbital roof [16, 18, 19]. It can result in proptosis, redness, and swelling around the eye, often resembling an infection [18, 19].

Our data demonstrated a wide range of presenting symptoms among patients. The most commonly reported symptom was periorbital swelling, observed in 55 cases, followed by proptosis in 23 cases and pain in 21 cases. Other symptoms included exophthalmos (8 cases), orbital mass (8 cases), visual impairment (7 cases), and headache (6 cases). Less frequently reported symptoms comprised diplopia, globe displacement, blurred vision, ocular discharge, and periocular erythema. Analysis of the data revealed that, among the 99 cases, five involved bilateral orbital involvement, while 48 were localized to the right orbit and 46 to the left orbit.

3.5. Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are the primary imaging modalities utilized for the diagnostic evaluation of orbital lesions, offering complementary information [20, 21]. Contrast-enhanced CT is particularly valuable for assessing the extent of soft tissue involvement within or adjacent to the orbit [16, 20, 21]. On conventional radiographs, lytic bone lesions often display irregular, serrated, or beveled margins, with or without a narrow zone of sclerosis. CT and MRI commonly reveal osteolytic lesions in orbital involvement cases, most

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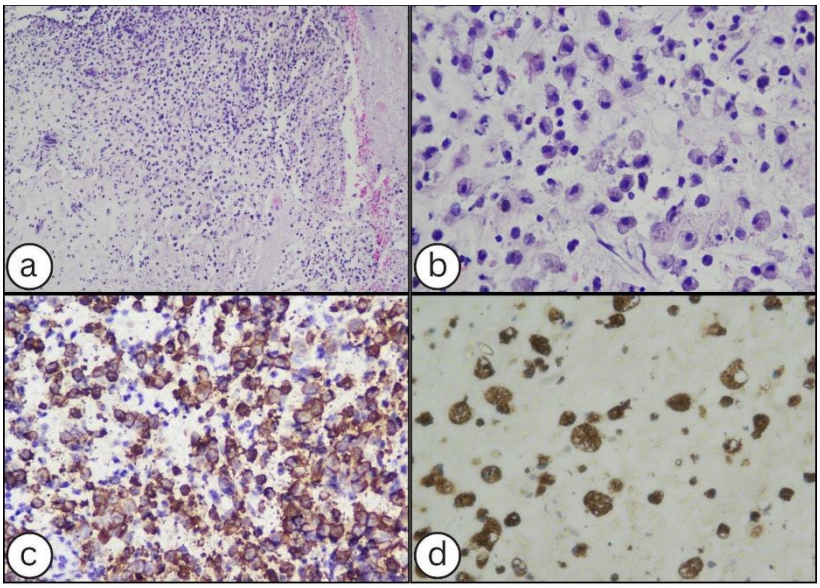

Figure 3. Histopathological examination (hematoxylin and eosin stain, **(a)** 100× **(b)** 400×) shows cells with round, pleomorphic nuclei, partially vesicular, with moderate to extensive cytoplasm, dense distribution of eosinophil cells, and diffuse immunoreactivity for CD1a **(c)** protein and **(d)** CD68**.**

frequently located in the superior or superotemporal orbital region [16, 20, 21].

MRI offers superior soft tissue contrast and high-resolution visualization of normal orbital structures [11, 20]. It is especially effective in detecting soft tissue masses, bone destruction, dural infiltration, and lesions affecting the hypothalamic-pituitary axis or surrounding brain structures [11]. Consequently, MRI is particularly suited for evaluating intracranial extension of Langerhans cell histiocytosis (LCH). Moreover, due to its lack of ionizing radiation, MRI is considered the imaging modality of choice for pediatric patients [11, 20, 21]. LCH lesions typically appear as heterogeneous bone-replacing masses. On T1-weighted images, they are isointense to iso-hypointense, while T2-weighted sequences reveal a mixed signal pattern ranging from hyperintense to hypointense. Following contrast administration, these lesions usually exhibit moderate to marked enhancement [11, 20, 21].

3.6. Biopsy, Histology, and molecular markers

A definitive diagnosis of Langerhans cell histiocytosis (LCH) can only be achieved through histopathological examination (HPE), typically performed via incisional or excisional biopsy [4, 17, 19]. Histological analysis reveals abnormal Langerhans cells interspersed with eosinophils and multinucleated giant cells. These pathological Langerhans cells differ from their normal counterparts by exhibiting a more rounded morphology and lacking the characteristic dendritic architecture. They also feature cytoplasmic vacuoles and indented nuclei [17, 19].

One of the hallmark ultrastructural features of LCH is the presence of Birbeck granules, which are pentalaminar, rod-shaped cytoplasmic inclusions with vesicular ends, identified in approximately 50–70% of cases through electron microscopy [4, 19, 20]. Immunohistochemically, LCH cells consistently express S-100 and CD1a and may also be positive for adenosine triphosphatase (ATPase), peanut agglutinin binding, alpha-mannosidase, langerin, and fascin [16, 17, 20]. A conclusive diagnosis is established by the demonstration of Birbeck granules on electron microscopy or by immunopositivity for the CD1a marker [4, 16, 17, 19, 20].

3.7. Therapy

Currently, there are no standardized guidelines for the optimal management of Langerhans cell histiocytosis (LCH), mainly due to its unclear pathogenesis and heterogeneous clinical presentation [5, 16]. As a result, treatment decisions are primarily based on the extent of the disease and the organs involved.

In the present analysis of 99 cases, treatment approaches varied considerably. Monotherapy was employed in several

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Table 1. Articles reviewed on Recurrent Orbital Langerhans Cell Histiocytosis

Author	Year	Age	Gender	Location	Presentation	Treatment	Recurrence
Amemiya	1981	61	M	Both	Eyelid swelling	Biopsy	NA
Banna & Olutola	1983	25	F	Right Eye	Proptosis	Biopsy	NA
Banna & Olutola [25]	1983	2	M	Right Eye	Proptosis	Biopsy	NA
Caccioti et al. [26]	2016	7	F	Left Eye	Edema, swelling	NA	NA
Carneiro et al.	2019	39	F	Right Eye	Pain, swelling	Surgery	No
Chen & Yang [27]	2012	13	M	Right Eye	Pain, exophthalmos	NA	NA
Cheung et al. [28]	2007	36	M	Right Eye	Pain, proptosis	Biopsy and surgery	No
Cheung et al.	2007	20	M	Left Eye	Headache	Radiotherapy	No
Cheung et al.	2007	26	M	Right Eye	Swelling	Surgery	No
Das et al.[29]	2017	28	F	Right Eye	Impaired vision, proptosis, pain, eyelid swelling	Not received	NA
Early et al.	1995	2	F	Right Eye	Exophtalmos	NA	NA
Erly et al.	1995	2	F	Right Eye	Proptosis	NA	NA
Erly et al.	1995	1.5	F	Left Eye	Swelling	NA	NA
Escardo-Paton et al.	2004	23	M	Left Eye	Pain	Biopsy and chemotherapy	Yes
Esmaili & Harris	2016	1.5	M	Left Eye	Eyelid swelling	Chemotherapy	Yes
Esmaili & Harris	2016	2.5	F	Right Eye	Eyelid swelling	Chemotherapy	No
Esmaili & Harris	2016	7	M	Right Eye	Eyelid swelling	Surgery and chemotherapy	No
Esmaili & Harris	2016	2	M	Left Eye	Eyelid swelling, pain	Surgery and chemotherapy	No
Esmaili & Harris	2016	1.5	F	Left Eye	Swelling	Surgery and chemotherapy	No
Feldman et al. [30]	1985	1.5	M	Right Eye	Eyelid swelling	Biopsy and surgery	No
Feldman et al.	1985	1.5	F	Left Eye	Eyelid swelling, pain	Biopsy and surgery	No
Furuta et al. [31]	1991	3	M	Right Eye	Eyelid swelling, proptosis	Surgery	No
Giovannetti et al. [32]	2009	18	M	Left Eye	Eyelid swelling	Surgery	No
Giovannetti et al.	2009	11	F	Right Eye	Eyelid swelling	Surgery	NA
Gross et al. [33]	1988	35	F	Left Eye	Eyelid swelling, pain	Surgery	No
Guler et al. [34]	2016	55	M	Right Eye	Headache, visual impairment, proptosis	Surgery	NA
Gündüz et al.	2007	1	F	Right Eye	Periocular edema	Surgery	No
Gündüz et al.	2007	1	M	Left Eye	Periocular edema, proptosis	Surgery	No
Harbour et al. [35]	1997	3	M	Right Eye	Exophthalmos	Radiotherapy	NA
Harnett et al. [36]	1988	32	F	Left Eye	Diplopia, proptosis, visual impairment	Radiotherapy	NA
Harnett et al.	1988	2	F	Left Eye	Eyelid swelling, proptosis	Radiotherapy	NA
Harris & Woo [37]	2003	5	M	Left Eye	Eyelid Swelling	Biopsy	No
Harris & Woo	2003	16	M	Right Eye	Eyelid Swelling, pain, blurred vision	Biopsy	No
Harris & Woo	2003	8	M	Left Eye	Eyelid swelling	Biopsy and surgery	No
Harris & Woo	2003	14	M	Left Eye	Eyelid swelling	Biopsy and surgery	No
Harris & Woo	2003	3	M	Right Eye	Eyelid swelling	Biopsy and surgery	No
Harris & Woo	2003	9	M	Right Eye	Eyelid swelling	Biopsy and surgery	No
Harris & Woo	2003	2	M	Right Eye	Mass	Biopsy and surgery	No
Herwig et al. [38]	2013	9	F	Right Eye	Contusion	Chemotherapy	No
Herwig et al.	2013	3	F	Right Eye	Eyelid swelling	Chemotherapy	No
Herwig et al.	2013	8	M	Left Eye	Swelling	Chemotherapy	NA
Herwig et al.	2013	1	M	Left Eye	Trauma	Chemotherapy	No
Herwig et al.	2013	0	M	Right Eye	Swelling	Chemotherapy	No
Heuer	1972	56	F	Left Eye	Pain, visual impairment, eyelid swelling	Surgery and radiotherapy	NA
Hurwitz & Faquin [39]	2002	15	M	Right Eye	Pain	Biopsy	NA

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Jain et al.	2001	0	F	Right Eye	Mass	Chemotherapy	Dead
Jakobiec et al. [40]	1980	14	F	Left Eye	Eyelid swelling, pain	Surgery	No
Jakobiec et al.	1980	8	M	Right Eye	Eyelid edema	Surgery and radiotherapy	No
Jakobiec et al.	1980	5	M	Left Eye	Eyelid swelling, globe displacement	Surgery and radiotherapy	No
Jakobiec et al.	1980	51	M	Left Eye	Eyelid swelling, pain	Surgery and radiotherapy	No
Jordan et al. [41]	1993	2	M	Left Eye	Proptosis, globe displacement	Chemotherapy	No
Kaddu et al. [42]	2010	7	M	Left Eye	Proptosis	NA	NA
Kahilogullari et al. [43]	2012	6	F	Right Eye	Pain, proptosis, mass	Surgery	No
Kaplan et al. [44]	1972	26	F	Left Eye	Exophthalmos	Radiotherapy	NA
Kashkouli & Shahrzad [45]	2014	25	M	Left Eye	Periocular edema, pain, globe displacement	Biopsy, surgery, chemotherapy	No
Kashkouli & Shahrzad	2014	45	M	Left Eye	NA	NA	No
Kashkouli & Shahrzad	2014	8	M	Right Eye	NA	NA	No
Key et al. [46]	2004	2.5	M	Left Eye	Eyelid swelling	Biopsy	No
Kindy-Degnan et al. [47]	1991	17	M	Right Eye	Eyelid swelling, pain	Biopsy and chemotherapy	No
Kramer et al. [48]	1997	2	F	Right Eye	Proptosis, periocular erythema	Biopsy and chemotherapy	No
Kramer et al.	1997	1.5	F	Left Eye	Periorbital swelling, discharge	Chemotherapy	NA
Kramer et al.	1997	2	F	Right Eye	Proptosis	Chemotherapy	NA
Levy et al. [49]	2003	3	F	Right Eye	Periorbital swelling, discharge	Surgery and chemotherapy	No
Ludmerer & Kissane	1981	50	M	Left Eye	Headaches, exophthalmos	NA	NA
Marcos et al.	2007	24	F	Right Eye	Eyelid swelling, pain	Surgery	No
Marcos et al. [50]	2007	16	M	Right Eye	Proptosis, eyelid swelling	Surgery	No
Mokal et al. [51]	2000	2	M	Right Eye	Eyelid swelling. proptosis	Surgery	No
Moore et al. [52]	1985	1	M	Left Eye	Eyelid swelling	Biopsy	No
Moore et al.	1985	2.5	F	Both	Proptosis	Biopsy and chemotherapy	No
Moore et al.	1985	8	M	Left Eye	Periorbital swelling	Radiotherapy	No
Nemet et al. [53]	2001	7	F	Right Eye	Mass	Biopsy and chemotherapy	NA
Nirankari et al. [54]	1957	7	M	Right Eye	Proptosis	Surgery	No
Oh et al. [55]	2025	8	F	Left Eye	Lid edema	Surgery and chemotherapy	NA
Rajendram et al. [56]	2005	17	M	Left Eye	Eyelid swelling	Biopsy	No
Richards et al.	2019	9	F	Left Eye	Eyelid swelling	Biopsy, chemotherapy	No
Rogers & Hiatt [57]	1968	11	M	Left Eye	Proptosis, visual impairment	Chemotherapy, Radiotherapy	No
Rootman et al. [58]	1984	7	F	Right Eye	Eyelid swelling	NA	NA
Sakata et al. [59]	2008	2	F	Both	Exophthalmos	NA	NA
Satoh et al. [60]	2012	22	M	Left Eye	Pain, visual impairment	None (spontaneous)	NA
Smith et al. [61]	1999	3	F	Left Eye	Eyelid swelling, pain	No treatment (spontaneous regression)	NA
Sokol et al. [62]	2009	28	F	Right Eye	Eyelid swelling, headache	NA	NA
Song et al. [63]	2003	9	M	Right Eye	Eyelid swelling, mass	Surgery and chemotherapy	No
Solid et al. [64]	1994	5.5	M	Right Eye	Eyelid swelling	NA	NA
Sovrea et al.	2017	21	M	Right Eye	Eyelid swelling	Surgery	No
Stromberg et al.	1995	16	M	Left Eye	Impaired vision	Radiotherapy	NA
Subramanian et al. [65]	2003	41	M	Left Eye	Swelling	Surgery, chemotherapy, and radiotherapy	No
Tran & Allen [66]	2020	4	F	Right Eye	Periorbital swelling	NA	NA
Trocme et al. [67]	1991	17	F	Right Eye	Eyelid swelling, headache	Radiotherapy	No
Trocme et al.	1991	16	M	Left Eye	Mass	Radiotherapy	No
Trocme et al.	1991	16	M	Right Eye	Swelling	Radiotherapy	No
Trocme et al.	1991	2	F	Left Eye	Swelling	Surgery	NA

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Ulivieri et al. [68]	2008	25	M	Left Eye	Headache, pain	Surgery	No
van Zyl et al. [69]	2015	40	F	Right Eye	Periorbital swelling	Biopsy and chemotherapy	NA
Werner et al. [70]	2003	0	M	Both	Proptosis	Chemotherapy and radiotherapy	NA
Wheeler [71]	1946	34	M	Right Eye	Eyelid swelling, pain	Surgery	NA
Wladis et al. [72]	2008	18	M	Left Eye	Periorbital swelling	Surgery and chemotherapy	No
Wood et al. [73]	1988	3	M	Both	Proptosis	Surgery, chemotherapy, and radiotherapy	No
Zausinger et al. [74]	2000	32	F	Left Eye	Exophthalmos	Surgery	No
Zollars et al.	1984	0	M	Left Eye	Exophthalmos, proptosis	NA	NA

Abbreviation: M: Male; **F:** Female; **NA:** Not Available.

cases: 9 patients underwent biopsy alone, 11 received chemotherapy, 10 were treated with radiotherapy, and 20 underwent surgery. Combination therapies included biopsy with surgery (8 cases), biopsy with chemotherapy (7 cases), and a single case involving biopsy, surgery, and chemotherapy. Additional combinations included chemotherapy with radiotherapy (2 cases), surgery with chemotherapy (7 cases), surgery with radiotherapy (4 cases), and surgery with both chemotherapy and radiotherapy (2 cases). Notably, spontaneous regression was documented in 2 cases.

Orbital LCH is generally associated with a favorable prognosis, which supports a conservative therapeutic approach when feasible [3, 4]. Incisional or excisional biopsy with curettage is typically the first-line intervention for isolated orbital lesions, as fine-needle aspiration is often inadequate for histopathological confirmation [3, 4, 22]. Complete surgical excision is usually unnecessary. In contrast, systemic chemotherapy and low-dose radiotherapy are generally reserved for multifocal or multisystem disease [5, 16, 22]. Additionally, low-dose radiotherapy has demonstrated efficacy in inducing remission in more aggressive or refractory orbital lesions [16, 22].

3.8. Recurrence

Out of 99 cases, 59 (60%) showed no recurrence, while only 2 (2%) experienced a recurrence. The remaining cases did not have available data on recurrence [23, 24].

4. DISCUSSION

Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X, is characterized by the proliferation of CD1a+ and langerin-positive cells, which closely interact with various other cells such as lymphocytes, eosinophils, macrophages, and multinucleated giant cells [6]. Advances in molecular profiling have shown that mutations in the gain-of-function of V-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF) and Mitogen-Activated Protein Kinase Kinase 1 (MAP2K1) genes are responsible for approximately 80% of the genetic driver changes in pediatric LCH cases [6, 22]. The mitogen-activated protein kinase (MAPK) pathway is the most dysregulated pathway in cancer, with the BRAFV600E mutation found in about 8% of all cancer types [22]. The BRAFV600E mutations are associated with younger age at diagnosis, higher prevalence of multisystem LCH, high-risk disease, skin involvement, central nervous system (CNS) involvement, and a higher risk of bone lesions. In contrast, MAP2K1 mutations are more commonly associated with single-system bone LCH [6].

In this case, the patient exhibited a three-year history of progressive left palpebral swelling and erythema that later evolved into ocular proptosis and inferonasal globe displacement. A presumed diagnosis of orbital abscess with fistula was made based on the clinical signs of redness, swelling, and intermittent eyelid itching. Histopathological examination later confirmed orbital involvement of LCH following prior brain surgery and completed chemotherapy. This aligns with a previous study that shows a significantly higher risk of recurrence in multifocal bone LCH than single bone involvement, with recurrence rates reported to be approximately sevenfold higher in the former [75].

LCH presents across a broad clinical spectrum, from isolated lesions affecting a single organ system to aggressive multisystem disease with vital organ dysfunction [1, 6]. Common presentations include lytic bone lesions [3, 4]. Orbital involvement, while rare, can present in both anterior and posterior compartments of the orbit and often mimics common infectious or inflammatory conditions such as orbital cellulitis [76]. Other clinical manifestations in the orbit include ptosis, exophthalmos, or proptosis [1, 5].

The development of a palpebral abscess in this patient may have arisen as a post-surgical wound infection or as a complication of immunosuppressive chemotherapy, although microbiological confirmation was not obtained. Chemotherapy can result in various adverse effects, including immunosuppression. Continuous exposure to

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cytotoxic agents weakens the immune system, compromising the body's natural defense mechanisms. As a result, patients undergoing chemotherapy are more vulnerable to infections, primarily due to the therapy's suppressive impact on neutrophil production [77]. Even though the orbital manifestations that appeared in our case initially suggested an infectious etiology, it was later identified as part of systemic LCH.

Radiological imaging plays a vital role in the evaluation of LCH. A computerized tomography scan (CT scan) or magnetic resonance imaging (MRI) typically demonstrates lytic bone lesions with associated soft tissue masses, though cases without bone destruction have been reported [1, 76]. 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) is an advanced imaging modality that combines metabolic and anatomical data to facilitate cancer detection [78]. It enables simultaneous assessment of glucose metabolism and lesion localization across the body, proving valuable in evaluating multisystem involvement. Although highly sensitive for tumor detection, FDG-PET lacks specificity for malignancy. Elevated glucose uptake in tumors is primarily attributed to increased expression of glucose transporters (e.g., GLUT1) and heightened activity of glycolytic enzymes such as hexokinase, distinguishing them from non-cancerous cells [78, 79]. MRI identified a mass in the left superior orbit and the right occipital condyle in this case. However, FDG-PET was not performed due to its unavailability at our institution, reflecting a common limitation in resource-constrained settings.

The diagnosis of LCH can only be confirmed by histopathological examination, which reveals pathological Langerhans cells with eosinophils and giant cells [19]. Microscopic examination may show an inflammatory pattern consisting of eosinophils, neutrophils, lymphocytes, and macrophages in addition to the Langerhans cells, often called eosinophilic granuloma [22]. A definitive diagnosis of LCH requires the demonstration of Birbeck granules (pentalaminar cytoplasmic rod-shaped inclusions) by electron microscopy in 50-70% of the lesions or CD1a positivity or the presence of CD207+ staining [1, 4, 22]. Our patient's diagnosis was confirmed using CD1a, consistent with established diagnostic protocols.

The treatment protocols for LCH are not yet standardized [5]. Current LCH treatment strategies are based on the extent of organ involvement. Curettage is often performed for single-system unifocal/isolated bone involvement [3, 4, 22]. Intracranial involvement in orbital lesions is considered a CNS risk factor and requires systemic chemotherapy [5]. The current standard of care for initial therapy involves a combination of vinblastine and prednisone for one year, with mercaptopurine added for high-risk LCH [2, 3, 5, 6]. In this case, the patient underwent surgery and was treated with a combination of vincristine, prednisone, methotrexate, and cyclophosphamide. Systemic therapy is preferred to minimize the risk of long-term complications, particularly in patients with bone lesions in the skull base and orbit [22]. Vinblastine and prednisolone are commonly used as induction therapy [6]. Curettage or intralesional steroid injections may induce long-term remission by inhibiting Interleukin-1 (IL-1) and Prostaglandin E2 (PGE2), thus mediating osteolysis [1]. Radiotherapy and bone marrow transplantation are considered in cases of recurrent or refractory cases, although excessive radiation doses to the head and neck can lead to significant long-term sequelae. Younger patients are more radiosensitive than adults and, therefore, more vulnerable to these effects. Immunoglobulin therapy has also shown benefits in cases of CNS involvement [1].

The identification of BRAF and MAP2K1 mutations in Langerhans cell histiocytosis (LCH) has expanded opportunities for targeted therapeutic approaches. BRAF-V600E inhibitors have shown encouraging results, particularly in patients with limited treatment options. Adults with severe or multisystem LCH currently lack a standardized therapy, and children with refractory or high-risk disease often experience poor outcomes [80].

Although emerging targeted therapies offer promising outcomes, such options were not utilized in our case due to the lack of molecular testing for MAPK pathway mutations and restricted access to targeted agents. In low-resource settings, cost constraints and limited infrastructure for genetic profiling remain substantial barriers. This limitation underscores the global disparity in access to precision oncology and reinforces the urgent need for broader implementation of molecular diagnostics and equitable access to novel therapies.

This case illustrates the diagnostic challenges and treatment limitations associated with recurrent multifocal Langerhans cell histiocytosis (LCH) with orbital involvement, particularly in low-resource environments. Early diagnosis, access to molecular testing, and coordinated multidisciplinary care are essential for improving patient outcomes in such complex cases.

5. CONCLUSION

Langerhans Cell Histiocytosis (LCH) is a rare and complex disorder with a broad spectrum of clinical manifestations that vary greatly depending on the organs affected and the extent of disease involvement. Orbital involvement is one of the uncommon presentations of LCH and necessitates a

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comprehensive clinical assessment, supported by advanced radiological imaging and histopathological examination, to establish an accurate diagnosis. Early and accurate diagnosis is crucial, as delayed recognition and management of the disease can result in significant and potentially irreversible damage to affected organs, ultimately impacting the patient's long-term prognosis and quality of life. Although LCH can lead to serious complications if not promptly treated, recurrence of the disease is relatively rare. Nevertheless, long-term follow-up is recommended to ensure early detection of any potential relapse and to maintain optimal patient outcomes.

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Ethical statement

This research did not involve ethical considerations. The patient's information was confidential, and consent was obtained during the investigation.

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