Original Article

# Clinical spectrum and management outcomes of Langerhans cell histiocytosis of the orbit

*Kirthi Koka, Md. Shahid Alam[1], Nirmala Subramanian, Krishnakumar Subramanian[2], Jyotirmoy Biswas[2], Bipasha Mukherjee*

**Purpose:** To describe the clinical spectrum and management outcomes of Langerhans cell histiocytosis (LCH) involving the orbit. **Methods:** Retrospective review of patients with orbital LCH presenting at the Sankara Nethralaya, Chennai, India, over the past 15 years. Demographic details, presenting features, radiology, histopathology, immunohistochemistry, and management outcomes were analyzed. **Results:** Nine patients were reviewed. The mean age of presentation was 10.12 ± 14.31 years (range: 6 weeks to 35 years). Eyelid swelling was the most common presenting feature (4, 44.4%), followed by proptosis (3, 33.3%). The mean duration of the presentation was 2.21 ± 2.77 months. Radiological investigations revealed orbital roof osteolytic defects in six (66.6%) patients. Six patients underwent near-complete excision of the mass while three underwent incisional biopsy. Histopathology revealed histiocytes with nuclear grooving and numerous eosinophils characteristic of LCH. The cells were positive for CD1a and S 100 antigens. None of the patients had any systemic involvement. Three received systemic steroids and four received systemic chemotherapy. At a mean follow-up of 17.85 ± 23.46 months, all had complete remission without any signs of recurrence. One patient was lost to follow-up after near-complete excision while one adult patient with a mass in the intraconal space had no recurrence after near-complete excision. **Conclusion:** LCH is a rare disorder of the orbit that commonly occurs in children and should be considered a differential for osteolytic lesions involving the orbit. All patients should undergo a systemic evaluation to rule out multifocal disease. The treatment depends upon disease extent and risk factors.

**Access this article online**

**Website:** www.ijo.in

**DOI:** 10.4103/ijo.IJO_1375_19

**Quick Response Code:**

**Key words:** Langerhans cell histiocytosis, orbit, osteolytic orbital lesion

Langerhans cell histiocytosis (LCH) is an uncommon disorder characterized by the proliferation of pathologic Langerhans cells of the monocyte-macrophage lineage or dendritic system. Historically referred to as "Histiocytosis X," an umbrella term which encompasses a spectrum of diseases including, Eosinophilic granuloma (unifocal disease), Hand–Schuller–Christian disease (multisystem disease) and Letterer–Siwe disease (acute fulminant multisystem disease), this entity has now been reclassified as LCH by the Histiocytic Society.[1] Orbital LCH constitutes about 1% of all orbital tumors, most often presenting as unifocal-single system disease.[2] However, it can progress to a multisystem disorder. Current classification schemes determine prognosis based on the disease extent and involvement of risk organs.

Treatment of orbital LCH is undetermined with multiple reports stating successful outcome following minimal surgical intervention and intralesional corticosteroid injection.[3-7] The LCH III protocol considers orbital disease as a "central nervous system (CNS) risk" lesion which should be treated with systemic chemotherapy to prevent the development of CNS complications.[3] However, there is minimal literature supporting the role of systemic chemotherapy for the unifocal orbital disease. The present study aims to describe the clinical and histopathological spectrum of LCH of the orbit and outcomes of different treatment modalities.

## Methods

A retrospective record review of all patients diagnosed with orbital LCH from 2000 to 2016 at the Medical Research Foundation, Sankara Nethralaya, Chennai, India, was performed. The study adhered to the tenets of the Declaration of Helsinki and institutional review board approval was obtained. All patients gave consent for publication of clinical photographs and related documents for research purposes.

Nine histopathologically proven cases of LCH were included in this study. Demographic details including age, gender, and laterality were recorded. The clinical findings,

Orbit, Oculoplasty, Reconstructive and Aesthetic Services,Sankara Nethralaya, Medical Research Foundation, Chennai, Tamil Nadu, [1]Orbit, Oculoplasty, Reconstructive and Aesthetic Services, Aditya Birla Sankara Nethralaya, Kolkata, West Bengal, [2]Larson and Turbo Department of Ocular Pahthology, Vision Research Foundation, Sankara Nethralaya, Chennai, Tamil Nadu, India

Correspondence to: Dr. Md. Shahid Alam, Orbit, Oculoplasty, Reconstructive and Aesthetic Services, Aditya Birla, Sankara Nethralaya, Kolkata, West Bengal (A Unit of Medical Research Foundation, Chennai), India. E-mail: mshahidalam@gmail.com

Received: 26-Jul-2019 Revision: 03-Oct-2019
Accepted: 11-Feb-2020 Published: 24-Jul-2020



**Cite this article as:** Koka K, Alam MS, Subramanian N, Subramanian K, Biswas J, Mukherjee B. Clinical spectrum and management outcomes of Langerhans cell histiocytosis of the orbit. Indian J Ophthalmol 2020;68:1604-8.

imaging features, type of surgery performed, histopathological, and immunohistochemistry findings were documented. All patients were referred to a pediatric oncologist to rule out systemic disease. Detailed documentation of the management and follow-up was done.

The data reviewed were maintained using Microsoft Excel and analyzed using Microsoft Excel 2013 (Microsoft Corp, Redmond, WA).

## Results

There were a total of nine patients with a mean age of 10.12 ± 14.31 years (range: 6 weeks to 35 years) [Table 1]. Five (55.5%) cases were males while four (44.4%) were females. The right eye was involved in five cases, while four cases had left-sided involvement. None of the patients had bilateral involvement.

The mean duration of presenting symptoms was 2.21 ± 2.77 months (range: 3 days to 9 months). The most common presenting symptom was lid swelling ($n$ = 4) followed by the prominence of the eyeball ($n$ = 3) [Fig. 1a]. Two patients presented with both lid swelling and prominence [Fig. 1a]. Five out of nine patients complained of pain at the time of presentation.

All patients underwent radiological imaging; computed tomography (CT) scan was done in seven patients and magnetic resonance imaging (MRI) in two. Characteristic osteolytic punched out bony lesion involving the superior orbital rim and roof was noted in six (66.6%) patients [Fig. 1b]. Two of these six patients had erosion of the orbital roof with adjacent dural encroachment. Each of the remaining three patients showed soft tissue lesion in the superior extraconal, medial extraconal, and intraconal space with no bony involvement.

Six patients underwent near-complete excision of the mass while an incisional biopsy was done in the rest three.

Histopathological examination revealed classical Langerhans cells with grooved nucleus along with a dense collection of eosinophils, suggestive of LCH [Figs. 1c and 2a, b]. The diagnosis was confirmed by immunohistochemistry, which showed positivity to S-100 and CD 1a antigens [Fig. 2c and d].

All patients were referred to a pediatric oncologist to rule out systemic involvement. None of the patients in the study group had additional systemic involvement thus confirming the diagnosis of unifocal orbital LCH.

Among the nine patients in our study, three patients received systemic steroids in the form of long term oral steroids ($n$ = 2) and pulse therapy with intravenous methylprednisolone ($n$ = 1). Four patients received six cycles of systemic chemotherapy along with steroids which comprised vinblastine ($n$ = 1), 6-mercaptopurine ($n$ = 1), and vincristine ($n$ = 2). All four of these cases had erosion of the orbital roof with two patients having dural encroachment and the other two having soft tissue lesion in the superior extraconal space. The mean duration of treatment was 3.85 months (range: 3 days to 6 months).

One patient with an intraconal mass lesion who underwent near-complete excision received no further intervention and was advised observation.

One patient who was referred to the oncologist was lost to further follow-up. The remaining eight patients were followed up for a mean duration of 17.85 ± 23.46 months (range: 2–72 months) after completion of treatment. At the last follow-up, all eight patients had complete resolution with nil orbital or systemic recurrence [Fig. 1d-f].

## Discussion

LCH is a benign idiopathic disorder of histiocytic origin. The disease has a slight male predominance with maximum occurrence noted between 1 and 4 years of age.[8]

It can manifest either as a single system (unifocal or multifocal) or multisystem disease.[9] Orbital involvement occurs in 1–20% of the cases in the form of unifocal-single system disease, which in turn corresponds to only 1% of all orbital tumors.[10]

**Table 1: Clinical and management details**

| Pt. No | Age | Sex | Duration of symptoms | Eye involved | Presenting features | Location of lesion on imaging | Management | Follow-up (Months) |
|---|---|---|---|---|---|---|---|---|
| 1 | 35 years | M | 2 weeks | OD | Lid swelling, proptosis | Superior extraconal space | Incision biopsy + ST (60 mg weekly tapering)-7 weeks | 8 |
| 2 | 4 years | M | 2 months | OD | Lid swelling | Orbital roof + dural encroachment | Excision biopsy + 6 MP (6 cycles)-6 months | 8 |
| 3 | 8 years | M | 3 months | OD | Lid swelling | Superior orbital rim + roof | Excision biopsy + ST-6 months | 72 |
| 4 | 13 months | F | 3 months | OS | Lid swelling, proptosis | Superior orbital rim + roof | Excision biopsy | LTF |
| 5 | 5 years | F | 2 weeks | OD | Proptosis | Orbital roof+dural encroachment | Excision biopsy + VCR (6 cycles)-6 months | 2 |
| 6 | 6 weeks | F | 3 days | OS | Lid swelling | Ill-defined lesion, Medial extraconal space | Incision biopsy + IVMP pulse therapy-3 days | 11 |
| 7 | 35 years | F | 9 days | OD | Proptosis | Ill-defined lesion, Intraconal space | Excision biopsy + observation | 5 |
| 8 | 11 months | M | 9 months | OS | Proptosis | Superior orbital rim + superior extraconal space | Excision biopsy + VCR (6 cycles)-6 months | 7 |
| 9 | 2 years | M | 1.5 months | OS | Lid swelling | Superior orbital rim + superior extraconal space | Incision biopsy + OS and VB (6 cycles)-6 weeks | 30 |

M: Male; F: Female; OD: Right eye; OS: Left eye; 6 MP: 6 mercaptopurine; VCR: Vincristine; VB: Vinblastine; IVMP: Intravenous methylprednisolone; ST: Oral steroids; LTF: Lost to follow-up

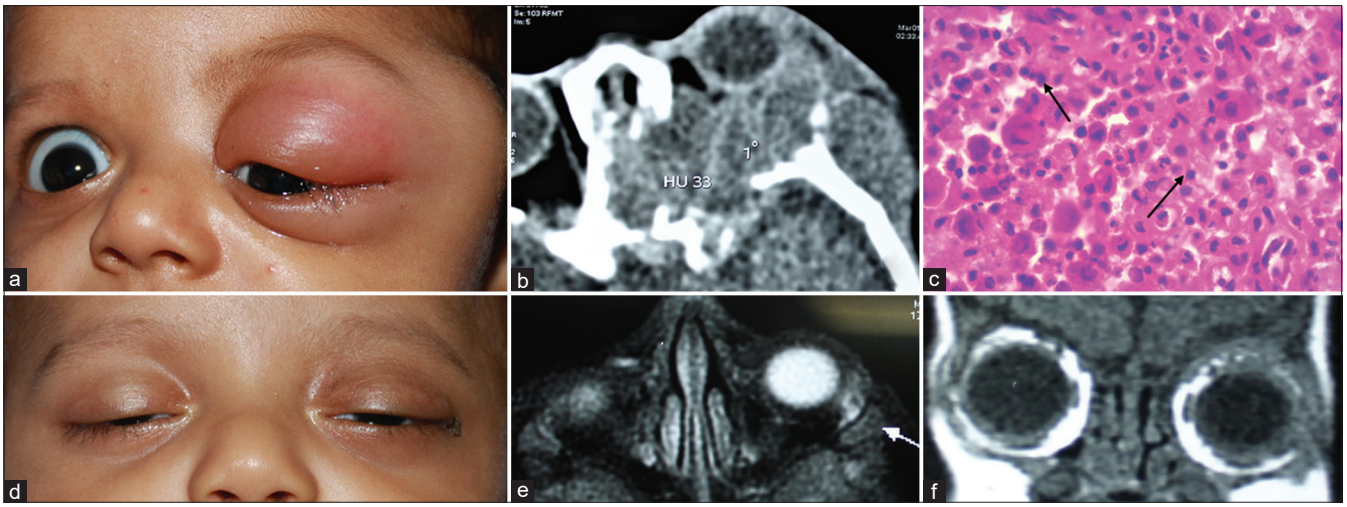


**Figure 1:** (a) A 2 years old boy presented with a left upper eyelid swelling resulting in mechanical ptosis. Palpation revealed a firm mass in the supero-temporal quadrant. (b) CT scans, axial view showing punched out a lytic lesion on the roof of the left orbit with soft-tissue mass (white arrow). (c) Microphotograph showing numerous multinucleated giant cells, Langerhans cells with characteristic membrane grooving and eosinophils (black arrows) (d) Clinical photograph showing resolution of eyelid swelling following surgery and systemic chemotherapy. (e and f) MRI images axial and coronal cuts showing near complete resolution of the mass

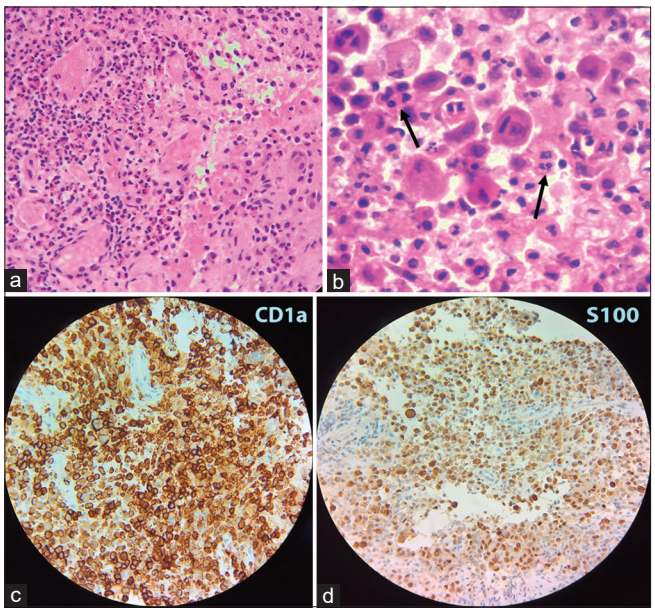


**Figure 2:** Microphotograph (hematoxylin and eosin stain, (a) 10 × and (b) 20×) showing numerous multinucleated giant cells, Langerhans cells with characteristic membrane grooving of the eosinophils (arrows), and showing diffuse immunoreactivity for S-100 and CD1a protein (c and d)

In our study, we found no sex predilection. Seven (77.7%) patients belonged to the pediatric age group. Though orbital LCH is predominantly a disease of the pediatric population, Cheung *et al*. reported three cases of orbital LCH in adults.[11] We also had two adults in our study group.

The most common site of involvement in the orbit is the part of frontal bone forming the superior orbital rim and roof. It can present as an isolated osteolytic lesion or with associated soft tissue mass in the orbit and surrounding tissue.[11] Active hematopoietic marrow occurs in the marrow space of the frontal bone. This space progressively contracts as the frontal sinus expands and is limited to the lateral orbital roof. This is the only space with active marrow after 8 years of age, thus, explaining the maximum occurrence of disease along the superolateral roof. In accordance with the literature, our study too showed orbital roof as the most commonly involved site.

The greater wing of sphenoid occasionally retains active marrow until the second decade of life which explains this being the site of LCH in adults, as noted by Cheung *et al*.[3,11] However, the two adult patients in our study had isolated masses in the superior extraconal and intraconal spaces, respectively, without any involvement of the superior orbital rim and sphenoid bone.

Based on the site of involvement and disease extent, patients present to the ophthalmologist with proptosis, eyelid mass, or ptosis. Soft-tissue lesions invading the orbit can also result in diplopia, nerve palsies, and optic disc edema.[8] Atypical presentation in the form of periorbital cellulitis has also been reported.[12]

The imaging modality of choice is CT which shows characteristic punched out lytic lesion with moth-eaten appearance.[13] Associated bony erosion results in the expansion of soft tissue lesions into the orbit and periorbital spaces.[14] It has been postulated that the pathological Langerhans cells release interleukin 1 and prostaglandin E2 which stimulate osteoclasts and result in bone resorption.[4] During the resolution phase, the affected bone undergoes sclerosis and with time is replaced by normal-appearing bone.[4]

Based on the involvement of bone and soft tissue components, the differentials in children are granulocytic sarcoma, inflamed dermoid, tubercular osteomyelitis, fibro-osseous lesions, and metastasis. In adults, lacrimal gland malignancies, meningioma, cholesterol granuloma, or inflamed dermoid are some of the differentials.

Confirmatory diagnosis can be obtained only on histopathological examination (HPE). HPE shows pathological Langerhans cells admixed with eosinophils and giant cells. These cells differ from the normal Langerhans cells in being more round and lacking the typical dendritic architecture. They have cytoplasmic vacuoles with the indented nucleus. Birbeck granules are cytoplasmic inclusions seen in 50–70% of the lesions. They are rod-shaped, pentalaminar structures

with vesicular ends and can be appreciated only on electron microscopy. They play a role in antigen presentation and are considered pathognomonic of LCH.[8] None of the patients in the present case series underwent electron microscopic evaluation.

Immunohistochemistry helps in further confirming the diagnosis and differentiating it from other histiocytic disorders. LCH cells are positive for S-100 and CD1a markers. They also stain positive for adenosine triphosphate, peanut lecithin binding, alpha-mannosidase, langerin, and fascin.[8]

The International Histiocytic Society has laid down criteria to establish the diagnosis of LCH. As per the criteria, two or more of the following are necessary to confirm the diagnosis of LCH: Positive staining for

1. Adenosine triphosphate
2. S-100 protein
3. Alpha mannosidase
4. Peanut lectin binding.

Definitive diagnosis requires demonstration of Birbeck granules by electron microscopy or CD1a positivity.[15]

LCH is known to involve multiple organs such as skin, bone, liver, spleen, lung, and CNS.[16,17] Patients with the unifocal disease at presentation can develop multifocal lesions with time. Also, the literature states an association between orbital LCH and development of diabetes insipidus (DI) as a late sequel. Hence, a thorough systemic evaluation is mandatory following histopathological confirmation, since treatment and prognosis depend on the extent of disease. Systemic evaluation should include complete hemogram, liver function test, coagulation profile, urine analysis and osmolarity, water deprivation test, chest X-ray, bone marrow analysis, and a complete skeletal survey.[18]

In our study, all nine patients were subjected to extensive systemic evaluation as advised by the pediatric oncologist. None of the patients showed systemic disease at the time of presentation. Similarly, nil systemic involvement at diagnosis was reported by Herwing *et al*. in their review of five cases and Cheung *et al*. who reported three cases of orbital LCH in adults.[8,11]

Patients with unifocal disease have a better prognosis compared to multisystem disease. Orbital LCH with intracranial extension has been classified as single system disease which generally carries a good prognosis.[14]

A review of the literature shows that there is no defined protocol for the treatment of orbital LCH. [Table 2] Different treatment modalities described for patients with the unifocal disease include observation, biopsy and curettage, excision with intra-lesional steroid, radiation, and high-dose systemic steroid with chemotherapy.[19]

Spontaneous resolution of the LCH lesion has been reported in the literature. Smith *et al*. reported a case of spontaneous regression of orbital lesion following CT-guided fine-needle aspiration cytology.[7] Similar reports of spontaneous regression following orbital biopsy and curettage have been reported by Rajendram *et al*. and Glover *et al*.[6,13] Harris and Woo state that small alterations in the microenvironment can disrupt the pathological cascade and induce regression.[4]

Harris *et al*. treated four out of seven cases with intralesional steroid post-excision and reported nil recurrence after a follow-up period of 6–24 months.[4] They state that recurrence post-excision can be overcome with an intralesional steroid (125 mg of methylprednisolone) which inhibits IL-1 and PGE2-mediated osteolysis.

Recurrence or progression following initial surgery can be tackled with low dose radiation therapy (400–1000 cGy).[6] Das *et al*. documented regression with nil recurrence at 4 years of follow-up in an 8-year-old girl with orbital LCH who received 1500 cGy in three fractions.[19]

Treatment protocols for patients with multiple foci/multisystem diseases are as per the guidelines laid down by the LCH III protocol. This protocol categorizes patients into three groups namely;[3]

1. Group 1: Multisystem "risk" patients with involvement of one or more "risk" organs (i.e. hematopoietic system, liver, spleen, or lungs)

**Table 2: A brief review of previously reported literature on management outcomes of Langerhans cell histiocytosis (LCH)**

| Study | No. of cases | Mean age (years) | MC presenting complaint | IHC | Management | Mean treatment duration | Mean follow-up | Recurrence |
|---|---|---|---|---|---|---|---|---|
| Harris *et al*.,[4] 2003 | 7 | NA | NA | NA | Surgery RT (2) Curettage + ILS (4) Curettage (1) | NA | 11.7 months | Nil |
| Cheung *et al*.,[11] 2006 | 3 | 27 | Orbital pain, swelling | S-100, CD1a (2), CD 1a (1) | Surgery (1) Surgery + RT (2) | NA | 2.1 years | Nil |
| Das *et al*.,[19] 2009 | 3 | 6 | Periocular swelling | S 100 + | Curettage + RT (1) Curettage + RT + CT - (1) Biopsy + CT + oral steroids (1) | NA | 4.5 years | Nil |
| Herwig *et al*.,[8] 2013 | 5 | 4.3 | Trauma, Periocular swelling | S 100 (1), S 100, CD 1a (2) | Surgery (1), Surgery + CT (4) | 7.25 months | 5.3 years | Nil |
| Esmaili *et al*.,[20] 2016 | 6 | 2.8 | Periocular swelling | CD 1a+ | Surgery (1) Curettage + ILS (1) Curettage + ILS + CT (3) Curettage + CT + BMT (1) | 29.3 weeks | 65.5 months | 1 case |
| Singh *et al*.,[22] 2016 | 8 | 8 | Upper lid swelling | S100, CD 1a, CD 68+ | Curettage + ILS (4) Incisional biopsy + ILS (4) | NA | 30 months | Nil |
| Present study | 9 | 10.1 | Lid swelling, Prominence of eyes | S 100, CD 1 a + | Surgery (2) Surgery + steroids (3) Surgery + CT (4) | 3.85 months | 17.85 months | Nil |

MC: Most common; IHC: Immunohistochemistry; NA: Not available; RT: Radiotherapy; CT: Chemotherapy; ILS: Intralesional steroid; BMT: Bone marrow transplantation

2. Group 2: Multisystem "low-risk" patients with multiple organs involved but without the involvement of "risk" organs
3. Group 3: Single-system "multifocal bone disease" and localized "special site" involvement such as "CNS-risk" lesions with the intracranial soft-tissue extension of vertebral lesions with intraspinal soft-tissue extension.

Orbital LCH is considered a CNS risk lesion. This means that patients with orbital LCH are at risk of developing DI as late sequelae. Though the multisystem disease is an independent risk factor for DI, there is no data to conclude that unifocal orbital LCH can progress to CNS-LCH with time.

Margo *et al*. studied 17 cases of orbital LCH and none of them progressed to CNS-LCH.[1] Harris *et al*. reviewed 62 cases of LCH with DI. Among the 62 cases, 12 patients demonstrated orbital foci as part of multisystem disease. None had isolated orbital lesions.[5]

Esmaili *et al*. reviewed 806 patients with CNS-LCH and observed no case of unifocal orbital LCH progressing to CNS-LCH.[20] Grois *et al*. analyzed all patients enrolled in the DAL-HX 83, DAL-HX 90, LCH I and LCH II studies, and on multivariate analysis, the orbital lesions could not be attributed as a risk factor for the development of CNS disorder or DI.[21] Moreover, there is no direct evidence to prove that chemotherapy in unifocal orbital lesions prevents progression to CNS-risk LCH. The reason why even LCH IV continues to view an isolated unifocal orbital lesion as CNS-risk is possibly because of the association of the multisystem disease with orbital lesions.[20] As of now, there is considerable evidence to show that all such patients have done really well just with biopsy, subtotal curettage, and intralesional steroid.

In our study, all nine patients presented with unifocal orbital disease. One patient was treated by observation while three patients received systemic steroids following orbital biopsy. Four patients with orbital roof erosion received systemic chemotherapy with either 6-mercaptopurine, vincristine, or vinblastine as per the LCH III protocol by the pediatric oncologist. None of our patients either showed progression to CNS disease or developed DI during the mean follow-up period of 17.87 months.

## Conclusion

LCH is a rare disorder of the orbit and is most commonly seen in children. It should be considered as a differential diagnosis for osteolytic lesions involving the orbit. Histopathology and immunohistochemistry are essential for diagnosis. All patients should be managed in consultation with an oncologist and undergo meticulous workup to rule out systemic disease. An orbital biopsy followed by systemic chemotherapy is the current protocol for the management of orbital LCH. However, due to the lack of consensus on the appropriate modality of treatment, unifocal orbital LCH may be managed by local measures under close follow-up. A multicentric randomized control trial should be done to reach a consensus on the management of isolated orbital LCH and the need for chemotherapy.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

## References

1. Margo CE, Goldman DR. Langerhans cell histiocytosis. Surv Ophthalmol 2008;53:332-58.
2. Shields JA, Bakewell B, Augsburger JJ, Flanagan JC. Classification and incidence of space-occupying lesions of the orbit: A survey of 645 biopsies. Arch Ophthalmol 1984;102:1606-11.
3. Histiocyte Society. LCH III (2nd version): Treatment protocol of the Third International Study for Langerhan – cell Histiocytosis, January 2002.
4. Harris GJ, Woo KI. Eosinophilic granuloma of the orbit: A paradox of aggressive destruction responsive to minimal intervention. Trans Am Ophthalmol Soc 2003;101:93-103. Discussion 103–105.
5. Harris GJ. Langerhans cell histiocytosis of the orbit: A need for interdisciplinary dialogue. Am J Ophthalmol 2006;141:374-8.
6. Glover AT, Grove AS. Eosinophilic granuloma of the orbit with spontaneous healing. Ophthalmology 1987;94:1008-12.
7. Smith JH, Fulton L, O'Brien JM. Spontaneous regression of orbital Langerhans cell granulomatosis in a three-year-old girl. Am J Ophthalmol 1999;128:119-21.
8. Herwig MC, Wojno T, Zhang Q, Grossniklaus HE. Langerhans cell histiocytosis of the orbit. Five clinicopathologic cases and review of literature. Surv Ophthalmol 2013;58:330-40.
9. Broadbent V, Gadner H. Current therapy for Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998;12:327-38.
10. Moore AT, Pritchard J, Taylor DS. Histiocytosis X: An ophthalmological review. Br J Ophthalmol 1985;69:7-14.
11. Cheung N, Selva D, McNab AA. Orbital Langerhans cell histiocytosis in adults. Ophthalmology 2007;114:1569-73.
12. Levy J, Monos T, Kapelushnik J, Maor E, Nash M, Lifshitz T. Langerhans cell histiocytosis with periorbital cellulitis. Am J Ophthalmol 2003;136:939-42.
13. Rajendram R, Rose G, Luthert P, Plowman P, Pearson A. Biopsy-confirmed spontaneous resolution of orbital Langerhans cell histiocytosis. Orbit 2005;24:39-41.
14. Shetty SB, Mehta C. Langerhans cell histiocytosis of the orbit. Indian J Ophthalmol 2001;49:267-8.
15. Malone M. The histiocytosis of childhood. Histopathology 1991;10:105-19.
16. Subramanian N, Krishnakumar S, Babu K, Mohan R, Lakshmi KS, Biswas J. Adult onset Langerhans cell histiocytosis of the orbit-A case report. Orbit 2004;23:99-103.
17. Grana N. Langerhans cell histiocytosis. Cancer Control 2014;21:328-34.
18. Kramer TR, Noecker RJ, Miller JM, Clark LC. Langerhans cell histiocytosis with orbital involvement. Am J Ophthalmol 1997;124:814-24.
19. Das JK, Soibam R, Tiwary BK, Magdalene D, Paul SB, Bhuyan C. Orbital manifestations of Langerhans cell histiocytosis: A report of three cases. Oman J Ophthalmol 2009;2:137-40.
20. Esmaili N, Harris GJ. Langerhans cell histiocytosis of the orbit: Spectrum of disease and risk of central nervous system sequelae in unifocal cases. Ophthal Plast Reconstr Surg 2016;32:28-34.
21. Grois N, Pötschger U, Prosch H, Minkov M, Arico M, Braier J, *et al*. Risk factors for diabetes insipidus in langerhans cell histiocytosis. Pediatr Blood Cancer 2006;46:228-33.
22. Singh S, Kaliki S, Palkonda VAR, Naik MN. Langerhans cell histiocytosis of the orbit: A study of eight cases. Oman J Ophthalmol 2018;11:134-9.