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Langerhans Cell Histiocytosis of the Orbit:

Five Clinicopathologic Cases and Review of the Literature

Martina C. Herwig, MD^{1,2}, Ted Wojno, MD¹, Qing Zhang, MD¹, and Hans E. Grossniklaus, MD, MBA¹

¹Department of Ophthalmology, Emory University School of Medicine, Atlanta, GA, USA

²Department of Ophthalmology, University of Bonn, Bonn, Germany

Abstract

Langerhans cell histiocytosis (LCH) is a proliferation of Langerhans cells intermixed with inflammatory cells, in particular eosinophils, that may manifest as unisystem (unifocal or multifocal) or multisystem disease. Orbital involvement typically manifests as a solitary lesion that carries a favorable prognosis. Herein, we describe the clinical and histologic spectrum of LCH of the orbit on the basis of five cases. One patient exhibited multifocal unisystem disease, the other four patients presented with a localized process. The typical histologic features included numerous histiocytes with varying degrees of giant cell formation and scattered eosinophilic granulocytes. The presence of Langerhans cells was confirmed by CD1a and S100 immunostaining. Transmission electron microscopy exhibited characteristic intracytoplasmic Birbeck granules. The different ophthalmic manifestations of LCH and treatment strategies are reviewed in the context of previously reported cases. As LCH may solely involve the orbit, treatment is based on the degree of organ involvement. LCH has to be included in the differential diagnosis in tumors of the ocular adnexae, in particular in young children.

Keywords

Eosinophilic granuloma; Langerhans cell histiocytosis (LCH); Orbit

I. Introduction

Langerhans cell histiocytosis (LCH), previously called histiocytosis X, is a term describing a spectrum of proliferation of Langerhans cells that may manifest as unisystem (unifocal or multifocal) or multisystem disease. This entity was first described by Alfred Hand, Jr. in 1893. Varying manifestations of the disease have been described in the subsequent years as Hand-Schüller-Christian disease, Abt-Letterer-Siwe disease, and eosinophilic granuloma of bone that were all classified as “histiocytosis X” by Lichtenstein in 1953.¹ Nezelof et al. identified the Langerhans cell as predominant pathologic cell in the disease leading to the term “Langerhans cell histiocytosis” in 1987.² Additionally, a division of histiocytic

Corresponding Author Hans E. Grossniklaus, MD, Emory Eye Center, L.F. Montgomery Laboratory, BT 428, 1365 Clifton Road, Atlanta, Georgia 30322, USA, Phone: (+1) 404-778-4611, Fax: (+1) 404-778-4610, ophtheg@emory.edu.

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disorders into three classes was proposed: LCH (class I), non-LCH (class II), and malignant histiocytic disorders (class III). This classification was revised and nowadays dendritic cell-related disorders (class 1), macrophage-related disorders (class 2), and malignant disorders (class 3) are now recognized. LCH is by far the most common entity in class 1 histiocytic disorders. (<http://www.histiocytesociety.org/site/c.mqISL2PIJrH/b.3809123/k.BD72/Home.htm>)

A. Terminology

LCH represents a clonal proliferation of pathologic Langerhans cells.^{3–5} LCH is further defined by unisystem (unifocal or multifocal) or multisystem disease. A localized infiltrate involving only the orbit (unisystem, unifocal) or, as our case 3, involving the orbit and other bones including the skull and leg (unisystem, multifocal) was formerly referred to as eosinophilic granuloma or eosinophilic granuloma of bone. The triad of lytic defects in the skull, proptosis, and diabetes insipidus produced by multifocal bone lesions in somewhat older children had been termed Hand-Schüller-Christian disease. The term Abt-Letterer-Siwe disease was reserved for the acute and fulminant form of LCH that typically affects children less than two years of age and involves multiple organs systems with eczematous rash, hepatosplenomegaly, anemia, and lymphadenopathy resulting in a fatal outcome.^{1, 6} Liver, spleen and bone marrow are regarded as high-risk organ sites.⁷ Pulmonary LCH represent a polyclonal proliferation of Langerhans cells.

B. Epidemiology

Although LCH may be diagnosed at any age,⁸ LCH usually occurs in young children with a peak at the age of 1–4 years.^{9, 10} The incidence of LCH ranges from 2.6 – 8.9/10⁶ children per year although several studies have shown an incidence of approximately 4–6/10⁶ children per year in Europe.^{11–15} The incidence in children younger than 1 year of age is 9–15.3/10⁶ per year.^{11–14} In children older than 10 years, the incidence is lower (about 0.7–2.0/10⁶ per year). Unifocal and single-system disease dominates over multi-system disease in most studies.^{12, 14, 15} In particular, small children younger than 2–3 years of age suffer more often from multi-system LCH which harbors a more unfavorable outcome.^{11, 14, 16} Coexistence of LCH and hemophagocytic syndrome has been shown to be prognostically relevant as it usually occurs in younger children and is related to a less favorable outcome.¹⁷ LCH is more common in boys than girls.^{9, 11, 12, 14, 15, 18} LCH in boys is usually diagnosed at a higher age than in girls who present with more severe organ involvement.¹⁸ Caucasians seem to be more frequently affected than other races.^{14, 15, 18} However, our case series comprise African-American, Caucasian, and Hispanic patients. Some regard orbital involvement as uncommon,^{19, 20} while others reported relatively high incidence rates of orbital LCH (37.5% and 23%).^{21, 22} Orbital involvement is usually seen in patients with chronic lesions and uncommon in acute disseminated forms of LCH.²² In adults, the diagnosis of LCH is made at a mean age of 35 ± 14 years with a peak age ranging from 20 – 30 years.⁸

C. Pathogenesis

The pathogenesis of LCH is still unclear.²³ Although a clonal proliferation of Langerhans cells has been identified^{3–5}, LCH is not unequivocally regarded as a true neoplasm and may

represent an atypical immunoreaction.²³ There is also evidence that the severity of this disease is directly influenced by an immature aberrant immune system.²⁴ Another hypothesis assumes that the accumulation of Langerhans cells in LCH results from survival rather than uncontrolled proliferation, and is associated with the expansion of T-regs.²⁵ There is also some evidence for an aberrant immune interaction between the clonal proliferation of dendritic cells and T cells leading to a “cytokine storm”.¹⁰ Uncontrolled cytokine production induced by several factors including viral infections may also contribute to transformation of precursor cells into pathologic Langerhans cells.^{26, 27} However, as the cell cycle is obviously not blocked in LCH lesions and chromosomal instability was found in LCH as well, a neoplastic process cannot be completely excluded.²⁸

Although factors such as infections (such as EBV, CMV, HHV-6), genetic disorders, malignancies (medulloblastoma, retinoblastoma, medullary astrocytoma, glioma), seasonal and environmental influences have been implicated in the pathogenesis of LCH^{14, 15, 18, 19, 29, 30}, there is no evidence for one factor to play a pivotal role.^{9, 11, 14, 31} However, each single factor may influence the immune system and thus predispose somewhat to LCH. For many patients - including our series - a history of a minor orbital trauma has been reported.^{18, 32} These findings may be biased since children are prone to have minor trauma at the head, however, it may be also a factor that is able to trigger an immune response and predisposed children may subsequently develop LCH.

II. Ocular Manifestations of LCH

Our series of five patients with typical clinical and histologic features of LCH is illustrated in Figs. 1–5. The clinical features of these patients are shown in Table 1. Isolated orbital infiltrates are the most common manifestation of LCH of the ocular adnexa.^{33, 34} They usually occur in children, but may also affect adults.³⁵ One case of bilateral sequential orbital involvement has been reported.³⁶ LCH was also described in the eyelid^{37, 38}, conjunctiva³⁹, caruncle^{18, 40}, as an epibulbar nodule⁴¹, in the choroid,⁴² the optic chiasm⁴³, and the orbital apex and cavernous sinus manifesting as cavernous sinus syndrome.⁴⁴

LCH of the orbit usually presents as an isolated bone lesion with an associated soft tissue mass, although it can also be associated with multifocal or multisystemic disease.^{18, 33, 45, 46} It occurs predominantly in the superior or superolateral orbital roof and exhibits other features depending on the location of the Langerhans cell infiltrate such as a visible mass with ptosis and/or (erythematous) swelling if located in the anterior orbit. This may be misinterpreted as an infectious process. Proptosis is predominantly seen in lesions that involve the posterior orbit. This may be accompanied by diabetes insipidus and skull lesions forming the triad formerly called Hand-Schüller-Christian disease. Depending on the location and the size of the lesion as well as the infiltrated structures such as extraocular muscles ocular movement may be impaired resulting in diplopia and nerve palsies may occur. Visual acuity may be somewhat affected in young patients due to ptosis and the development of amblyopia.¹⁸ Fundus abnormalities such as optic disc edema, dilated venous channels, and macular edema, have been reported in eyes with orbital LCH (Table 2).⁴⁷

Diagnostic imaging, including computed tomography (CT) and magnetic resonance tomography (MRT)¹⁸ shows well-defined bony lesions with a classic “punched-out” lytic appearance that are often accompanied by soft tissue involvement in the orbit.^{24, 48} Lesions without bone erosions have also been reported.^{44, 46} As orbital lesions may be part of a multisystem disease,^{21, 49} a complete medical history and systemic work-up is mandatory to rule out a multisystemic manifestation for all orbital LCH lesions.²¹ A scheme for systemic evaluation is shown in Table 3.^{7, 21, 27, 34}

None of the patients in our series with orbital LCH suffered from disease recurrence or progression although it has been reported in other case series.^{18, 21} Recurrence/progression in patients with localized orbital lesions occurs most likely within 12–18 months of initial treatment. However, recurrences after a 13 and 16 year disease free intervals have been described.^{50, 51} One report describes an orbital recurrence 10 years after involvement of the jaw.⁵² Thus, follow-up examinations are recommended *at least* within 2–3 years after the initial treatment.²¹

Several studies point towards an association between orbital involvement and development of diabetes insipidus/CNS disease.⁵³ Since diabetes insipidus require aggressive treatment in patients with orbital LCH, this seems to contradict a favorable outcome in patients with localized orbital involvement.^{1, 54} It appears that patients with limited orbital involvement as initial manifestation of LCH have a good prognosis whereas those with extended orbital and periocular involvement may be more likely to develop diabetes insipidus. Similar conclusions regarding the location and size of orbital lesions and their association with neurodegeneration were made by Vosoghi and co-workers who investigated nine patients with orbital lesions that occurred predominantly in the context of multifocal bone or multisystemic disease.²¹ They concluded that the orbit reflects a spectrum of the disease and thus treatment should be based on variable factors such as location, size, and type of involvement (unifocal unisystem, multifocal unisystem, multisystem disease). In particular, a distinction between anterior and posterior LCH lesions may be helpful for risk group assignment.

III. Pathologic features of LCH

A. Histology

Histopathologically, the histiocytic infiltrate consists - despite its relatively benign-looking histologic features - predominantly of a clonal proliferation of pathologic Langerhans cells that resemble tissue macrophages rather than the typical dendritic shape of Langerhans cells in the skin.¹ The Langerhans cell infiltrate is accompanied by a varying amount of giant cells and eosinophils which are not mandatory for the diagnosis of LCH. Lymphocytes, plasma cells, polymorphonuclear leukocytes, macrophages (histiocytes) and varying amount of necrosis can be also present (Tables 1, 2; Figs. 1–5). The lesions are very often vascular and erythrocytes are frequently observed due to hemorrhage.⁶ Mitotic figures (MF) are occasionally found. In our series, mitotic figures were present in two of five cases. One lesion (unifocal disease; Fig. 5) exhibited only 1 MF/10 high power fields (HPF), the other orbital lesion (multifocal, unisystem disease; Fig. 3) exhibited 1 MF/HPF. Larger studies have shown that there is no correlation between the histologic features and the disease

severity.⁵⁵ Older lesions may exhibit foamy (xanthomatous) histiocytes as sign of lipidization. Thus, in some cases LCH needs to be distinguished from Erdheim-Chester disease. Some bony lesions may undergo spontaneous healing resulting in a fibrotic scar.⁶

B. Immunohistochemistry

The combination of immunopositivity for the neuronal marker S100 and CD1a (Table 2, Fig. 5), which is specific for Langerhans cells (and thymocytes) and is not expressed by macrophages, helps to confirm the diagnosis. Other immunohistochemical markers that may be positive in LCH include adenosine triphosphatase, peanut lectin binding, alpha-mannosidase, CD207 (Langerin), and fascin.^{1, 19, 34, 56}

C. Transmission electron microscopy

Small rod- or tennis racket-shaped bodies, called Birbeck granules, may be found in the cytoplasm of regular and pathologic Langerhans cells (Table 2, Fig. 1 and 5). Although only present in about 50–70% of the lesions, Birbeck granules are regarded as pathognomonic for LCH.^{57, 58} In lesions with Birbeck granules, they may be found in 2–29% of the pathologic Langerhans cells.⁵⁹ Charcot-Leyden crystals are sometimes also found in histiocytes in LCH.^{60, 61}

IV. Differential Diagnosis

The *clinical differential diagnosis* of ophthalmic LCH includes periorbital cellulitis, acute dacryocystitis, (ruptured) dermoid cyst, hematoma, inflammatory pseudotumor, pilomatrixoma, leukemia, sarcoma, metastatic neuroblastoma, rhabdomyosarcoma, and other tumors.⁶² Some of these lesions may be differentiated from LCH by the absence of lytic bony erosions that are typical for LCH.

The *histologic differential diagnosis* of LCH include giant cell reparative granuloma,⁶³ hemorrhagic cyst, cholesterol granuloma (cholesteatoma),⁶⁴ Erdheim-Chester disease,⁶⁵ giant cell aneurysma of bone, giant cell tumor, and histiocytic sarcoma. These entities exhibit histologic features, are composed of CD1a- macrophages (not CD1a+ Langerhans cells) and can be excluded from LCH by immunohistochemical staining. CD68+ macrophages may be also present in LCH, in particular if complicated by the hemophagocytic syndrome.

V. Treatment

As the pathogenesis of LCH is still unknown, treatment is empirical.¹⁸ The choice of therapeutic regime is based on disease severity and degree of systemic involvement.⁶⁶ Different treatment possibilities are shown in Table 4. In general, the diagnosis of LCH should be proven by a biopsy. Incisional and excisional biopsies are preferred over fine-needle aspiration biopsy because the latter might not provide enough material for a sufficient histologic diagnosis.²⁷ In cases of sequential multifocal lesions, *observation* is one option.⁶⁷

As single bone lesions have a far better outcome than multiple bone lesions and multiorgan disease,¹⁶ most physicians recommend *biopsy and curettage* for solitary orbital lesions,

although remission after incisional biopsy alone has been reported.^{18, 68, 69} Localized lesions of the caruncle and eyelid have also been successfully treated with an excisional biopsy.^{37, 40}

Careful *curettage/excision in combination with intralesional steroids* may be another effective treatment for primary unifocal lesions of the orbit^{27, 45, 70} and recurrent lesions.⁵² One study group observed the absence of recurrence in 20 patients with unifocal, unisystem bone lesions of the orbit treated with excision and curettage alone but recurrences occurred in 3 patients treated with excision and adjuvant chemotherapy (n=2) and excision and intralesional triamcinolone (n=1), respectively.¹⁸ Although different doses of steroids have been used, 125 mg methylprednisolone is recommended as it might have an inhibitory effect on osteolysis.^{27, 45} The favorable outcome of excision and curettage alone may be attributed to changes in the microenvironment leading to the disruption of the pathological cascade.^{27, 45} This observation highlights the paradox of an aggressive bone destruction in LCH and its response to minimal intervention. However, recurrences have been reported after this treatment and thus close follow-up is recommended.⁷¹

Radiation is predominantly used to treat recurrences.^{45, 46} Side-effects or long-term sequelae such as secondary neoplasms are still a concern with (low-dose) radiation therapy.

Chemotherapy is regarded as a treatment for multifocal/multisystem disease or recurrences.^{19, 66} The most common chemotherapeutic agents are vinblastine, prednisone, etoposide, and methotrexate in various combinations. Chemotherapy might be also considered for orbital lesions with dura involvement - as in our case 2.⁷² Some authors have treated aggressive LCH of the orbit and skull base with intracranial extension and cranial nerve involvement with surgical excision followed by radiation and chemotherapy.⁷³

Bone marrow transplantation and immunoglobulin therapy are reserved for uncontrolled disease recurrences and CNS involvement, respectively.^{74, 75} The Histiocyte society provides up-to-date information regarding the latest treatment strategies and clinical trials. Since these trials are mostly designed for multi-system disease and are not conducted by ophthalmologists, the interested reader may should refer to the more comprehensive publications regarding this topic.^{7, 76}

VI. Conclusion

Our cases exhibited the typical features of LCH such as a proliferation of pathologic Langerhans cells interspersed with giant cells and eosinophils. Immunohistochemical stains for S100 and CD1a and/or the presence of Birbeck granules by TEM supported the diagnoses. Biopsy of orbital lesions allows for a histopathological diagnosis and may be even curative in some cases. Based on clinical evidence from the literature, the treatment of solitary anterior orbital lesions with biopsy and curettage and - where required - intralesional methylprednisone alone appears justified and may prevent overtreatment with subsequent possible systemic side effects/complications from radiation or chemotherapy. An interdisciplinary approach is recommended to rule out multifocal or multi-systemic disease and develop an appropriate treatment strategy. Long-term surveillance is advisable to

adequately diagnose and treat recurrences. Future knowledge about the detailed pathogenesis and etiology of LCH may allow for more specific and selective therapies.

VII. Literature Search

The literature selection of this review included a PubMed database search (<http://www.ncbi.nlm.nih.gov/pubmed>) from 1950 to 2012. The literature search was conducted using combinations of the following keywords: Langerhans cell histiocytosis, histiocytosis X, eosinophilic granuloma, orbit, eye. Articles written in English, German, and Chinese were considered. Many case reports were included due to the relatively rare occurrence of this disease but we limited them to reports contributing new information about characteristics, (differential) diagnosis, or treatment of the disease. Some reports were excluded because the diagnosis of LCH could not be unequivocally retraced.

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Figure 1.

Clinical appearance of an 8-years-old patient with a superior temporal mass in the left orbit (A). Computed tomography (CT) demonstrating the orbital lesion with bone erosion (B). Histology of the lesion showing infiltrates composed of histiocytes, giant cells (C, arrow; H&E, 80x), eosinophils (D, arrow; H&E, 128x), and lymphocytes. Birbeck granules exhibiting the shape of tennis rackets were detected by transmission electron microscopy (E; TEM, 30000x).

Figure 2. Clinical appearance of a three-years-old patient with an erythematous eyelid swelling (A). CT revealing the orbital lesion with bone erosion (B). Histology showing sheets histiocytes (inset) intermixed with giant cells, lymphocytes, and a few eosinophils (C; H&E, 40x).

Figure 3.

Clinical appearance of a one-years-old patient with a mass in the anterior orbit (A). CT revealing bony erosion in the orbital rim (B), the tibia (C), and the skull (D). Histology showing sheets of histiocytes intermixed with giant cells (arrowhead) and eosinophils (arrow) (E; H&E, 40x).

Figure 4. Clinical appearance of an eight-months-old patient with a right facial erythematous swelling (A). CT showing with a mass in his right temporal inferior orbit (B, C). Histologic picture illustrating the histiocytic infiltrate interspersed with occasional eosinophils (D; H&E, 40x).

Figure 5.

Clinical appearance of a nine-years-old patient with a mass in the right upper orbit (A). CT demonstrating the orbital lesion with bone erosion (B). Histology illustrating the Langerhans cell infiltrate with giant cells and eosinophils (C; H&E, 40x). The Langerhans cells were positive for S100 (D; 40x) and CD1a (E; 40x). Birbeck granules were detected by TEM (F; 14000x).

Table 1

Clinical and histologic features of our 5 patients with LCH.

Case	Age	Sex	Race	History	Orbit	Site	Size [mm]	Bone Erosion	Eye Exam	MF [per HPF]	S100	CD1a	Systemic disease	TEM	Follow-up	Therapy
# 1	8 yrs	♂	AA	trauma (orbital contusion with progressive swelling)	superotemporal (lacrimal gland area)	OS	20x15	+	VA 20/20; limitation of gaze superotemporally (OS)	0	+	N/A	no	BG	N/A	N/A
# 2	3 yrs	♀	C	progressive eyelid swelling after trauma (minor fall)	superior, preseptal lesion	OD		+	full extraocular muscle movement	0	N/A	N/A	no	N/A	11 yrs w/o recurrence	etoposide (VP-16; 168 mg i.v. per week) over 12 weeks
# 3	1 yrs	♂	C	orbital trauma (prior to complaints)	anterior	OS	N/A	+	ptosis	1	N/A	N/A	bony erosions leg, skull	N/A	3 yrs w/o recurrence	etoposide (VP-16; 100mg i.v.) over 10 weeks + prednisone (5mg)
# 4	8 mo	♂	HA	right facial swelling, pretreatment with antibiotics	inferolateral	OD	14x19x18	+	VA 20/20; full extraocular muscle movement / no strabism	0	+	+	no	N/A	2 yrs w/o recurrence	low dose methotrexate + prednisone (5 mg, bid) over 1 year
# 5	9 yrs	♀	AA	trauma (orbital contusion), pretreatment with topical antibiotics	superolateral	OD	29x18x35	+	VA 20/25; full extraocular muscle movement / no strabism	0.1 = 1 MF / 10HPF	+	+	no	BG	under treatment	vinblastine (6mg/m ² i.v. per week) + 6-MP (15mg/m ² p.o. per week) + prednisone over 1 year

AA: African-American; C: Caucasian; HA: Hispanic-American; HPF: high power field; MF: mitotic figures; mo: months; TEM: transmission electron microscopy; yrs: years; BG: Birbeck granules; wo: without; N/A: not available

Table 2

Diagnostic clinical and microscopic features of LCH

<p>Clinical features</p> <ul style="list-style-type: none"> • Orbital mass (typically superior or superior-temporal) (Fig. 1, 3, 5) • Bony erosions (Fig. 1–5) • Proptosis, impaired ocular movement, ptosis, erythematous swelling
<p>Histologic features (Fig. 1–5)</p> <ul style="list-style-type: none"> • Pathologic Langerhans cells • Giant cells (Fig. 1, 3) • Eosinophils (not mandatory) (Fig. 4) • Lymphocytes, plasma cells, PMNs, macrophages, erythrocytes
<p>Immunohistochemistry</p> <ul style="list-style-type: none"> • S100 (Fig. 5) • CD1a (Fig. 5)
<p>Transmission Electron Microscopy</p> <ul style="list-style-type: none"> • Birbeck granules (Fig. 1, 5)

Table 3

Applicable tests for disease extension in LCH (according to ^{7, 21, 27, 34}).

Tests for disease extension in LCH

- MRT/CT (orbit)
- Physical exam
- X-ray skull (4 views)
- Complete skeletal bone survey X-ray and bone scan or PET scan
- Chest X-ray
- Imaging of abdomen, pelvis
- Bone marrow biopsy/aspiration
- Blood count with differential erythrocyte sedimentation rate
- Blood electrolytes and coagulation profile
- Liver function test (including serum albumin, AST, ALT, bilirubin, AP)
- Urine analysis and urine osmolarity
- Water deprivation test

Table 4

Treatment strategies of orbital LCH.

Treatment	Type of LCH	References
observation	LCH, diagnosed elsewhere (sequential multifocal LCH)	67
incisional biopsy (w/o curettage)	unisystem, unifocal LCH	68, 69
biopsy and curettage/complete excision	unisystem, unifocal LCH	18, 20, 45, 46, 72
subtotal curettage and intralesional methylprednisolone (30–125 mg)	unisystem, unifocal LCH (recurrence - 1 case report)	27, 45, 52
radiation (400–800cGy)	unisystem, unifocal LCH	27, 45, 46
chemotherapy (various combinations of prednisone, vinblastine, etoposide, methotrexate, 2-cda, 6-mercaptopurine)	unisystem, unifocal LCH with contact to the Dura Mater multifocal/multisystem LCH recurrent disease	19, 66, 71, 72, 77
surgical excision, radiation & chemotherapy	single report of “aggressive” LCH	73