CASE REPORT

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Solitary Langerhans histiocytosis of the orbit: case report and review of the literature

ALINA SIMONA ŞOVREA[1)], DANA MONICA BARTOŞ[2)], ADRIAN BARTOŞ[3)], ELEONORA DRONCA[4)], BIANCA AURORA SZABO[2)]

[1)]*Discipline of Histology, Department of Morphological Sciences, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*

[2)]*Discipline of Anatomy and Embryology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*

[3)]*Department of Surgery, "Prof. Dr. Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania*

[4)]*Department of Molecular Sciences, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*

Abstract

Langerhans cell histiocytosis (LCH), previously known as "histiocytosis X", is a clinical entity characterized by abnormal proliferation of Langerhans cells, which exert a mass effect. Orbital involvement due to LCH is rare as a unifocal disease, seldom occurring outside the pediatric population. We report a case of a 21-year-old man with solitary LCH of the orbit depicted by magnetic resonance imaging (MRI) and diagnosed by histopathological examination.

Keywords: Langerhans cell histiocytosis, histiocytosis X, eosinophilic granuloma, orbit, eye.

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease of unknown cause [1, 2]. It represents an abnormal proliferation of Langerhans cells (dendritic line bone marrow-derived antigen-presenting cells), intermixed with mainly eosinophilic cells [1]. The basic pathological feature of this disease is to form tumor masses or granulomatosis with destruction of the surrounding tissues [1].

Previously known as "histiocytosis X", it primarily involves bones but it can also involve other organ systems [1, 3–7]. LCH is actually a term that encompasses three related subtypes: acute disseminated LCH (Letterer–Siwe disease – soft tissues and visceral involvement with or without bone lesions), multifocal LCH (Hand–Schüller–Christian syndrome – a triad of exophthalmia, skull bone defects and diabetes insipidus), and unifocal LCH (also known as eosinophilic granuloma, which represents about 70% of LCH cases) [1, 3–10]. LCH is more common in children than in adults, most cases being diagnosed before the age of 15 [11, 12]. Large studies tend to demonstrate preponderance in males, sometimes as high as 60–70% of all the cases [11, 12]. The disease is more frequent in Caucasians of Northern European descent and it is rarer in Southern and Eastern Europe [4–6, 13].

The orbital localization is an uncommon condition (less than 1% of all orbital tumors and 23% of all LCH cases) [13–16], and most often represents a unifocal disease [13–16]; it can also be part of the multifocal form [7, 8, 10, 13, 15, 16], being seldom present in the acute multisystem variety of Letterer–Siwe syndrome (where probably represents a symptom derived from adjacent bone involvement) [17].

This paper presents a clinical and pathological description of a solitary Langerhans histiocytosis of the orbit, for the particularities of the case (the rarity of the condition, its appearance to a young Caucasian male, with no history of head trauma, the good evolution without recurrences, despite the very conservative treatment). The case was followed-up for four years; it was decided to be presented now, given the favorable development.

Case presentation

A 21-year-old Caucasian male presented with right intraorbital expanding mass in the superolateral region of the right orbit, which subsequently developed into partial swelling of the superior eyelid without visual changes or limitation of the movements of the eye (Figure 1a). Written informed consent was obtained from the patient for the publication of this case report and accompanying images; the patient also consented for samples prelevation to a protocol approved by the Medical Ethics Committee of "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania.

On examination, edema and erythema of the superior eyelid and minimal exophthalmos were noted. Antibiotic and anti-inflammatory treatment for a supposed orbital cellulitis had no result. Neurological and systemic examinations were within normal limits; hematology and biochemistry investigations were likewise, within normal limits.

Computed tomography (CT) scan of the brain with orbital view showed a well-delineated, non-encapsulated intraorbital mass located in the superolateral part of the orbit erosion of the lateral orbital wall (Figure 1b).

The tumor was completely surgically removed, the bone drilled to healthy structure. Prior to microscopic examination, tissue samples were immersed into 10% formaldehyde solution for fixation, and then embedded

into paraffin. For Hematoxylin and Eosin (HE) staining and immunohistochemistry (IHC), consecutive sections of 4 μm in thickness were prepared according to paraffin-sectioning technique. The specimens were examined using a Leica DM 750 microscope (Leica, Germany) at 20×, 40×, 100× magnifications and photographed with a Leica ICC 50 HD (Germany) camera connected to the microscope.

Histological examination performed in HE staining (Figure 2, a and b) revealed a rich vascularized fibro-adipose tissue and rich inflammatory aggregates, mostly consisting of clonal proliferation of pathological Langerhans cells (histiocytic-like cells with indented nuclei and abundant cytoplasm) and eosinophil-rich inflammatory cell infiltrate that also included mature lymphocytes and few scattered multinucleate giant cells. There was no nuclear pleomorphism and mitoses could not be demonstrated.

The IHC was decisive in establishing the diagnosis. Standard IHC staining Avidin–Biotin complex (ABC) method with 3,3'-diaminobenzidine (DAB) chromogen was performed, the coloration following the manufacturer's protocol. The Langerhans cells were labeled with anti-S100 protein monoclonal antibody MAB079-1 (clone 15E2E2) (Figure 3, a and b) and anti-CD1a monoclonal antibody (clone STJ190010) (Figure 3c), showing a strong cytoplasmic and nuclear immunoreactivity. The classic macrophages exhibited a variable immunopositivity for anti-CD68 monoclonal antibody (clone STJ96952) (Figure 3d). Control slides were included in each staining run; therefore, IHC positivity-expression was evaluated with respect to positive control cells. All immunohisto-chemical stainings were evaluated by two persons inde-pendently and consensus was made when the opinions differed.

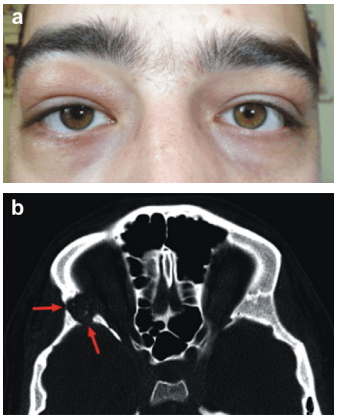

Figure 1 – ***(a) Photo of the patient on admission: right superior eyelid edema and erythema, with minimal exophthalmos (four weeks duration); (b) Brain CT scan – orbital view. Bone window shows the erosion of the lateral wall of the orbit (arrows).***

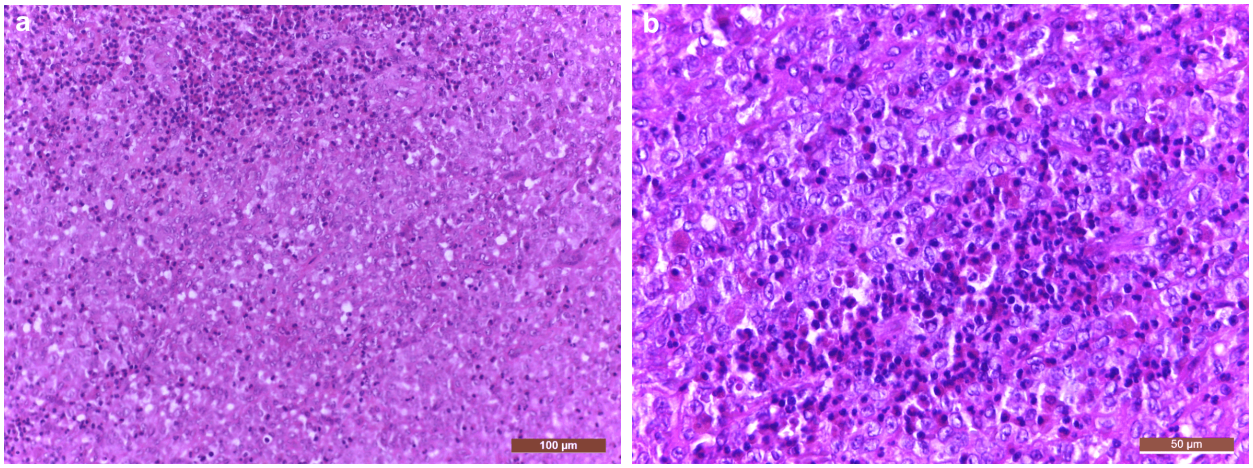

Figure 2 – ***(a) Infiltrative proliferation of intermediate-size, histiocyte-like Langerhans cells, with eosinophilic cytoplasm and indistinct border; (b) Langerhans cells with oval nuclei, indented or with longitudinal grooves, admixed with inflammatory cells, mainly eosinophils. HE staining: (a) ×100; (b) ×400.***

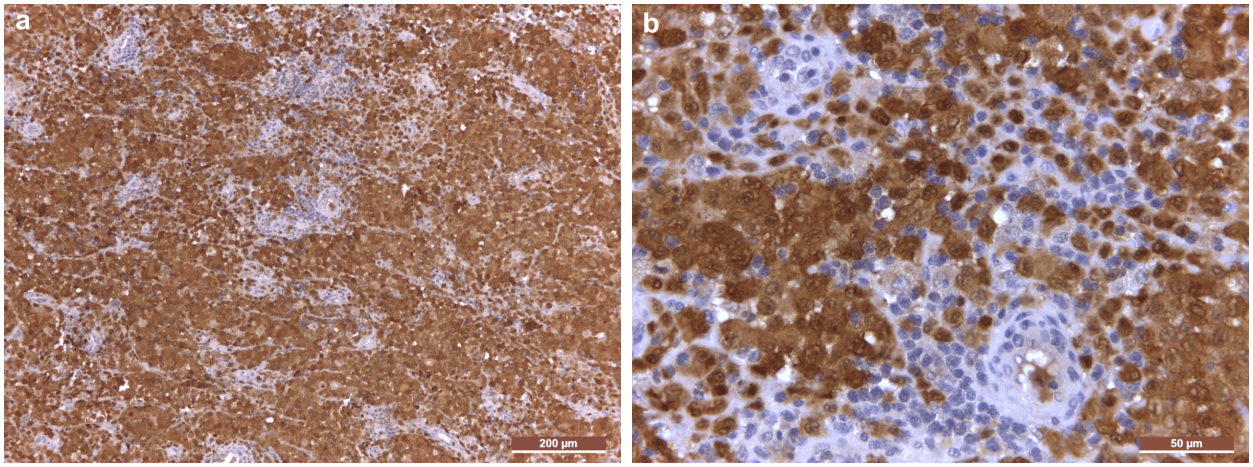

Figure 3 – ***(a) Immunohistochemistry of Langerhans cells with intense S100 expression (×100); (b) Immunohisto-chemistry of admixed S100-negative inflammatory cells (×400). Brown staining of the nuclei and/or cytoplasm equals positive immunohistochemical expression.***

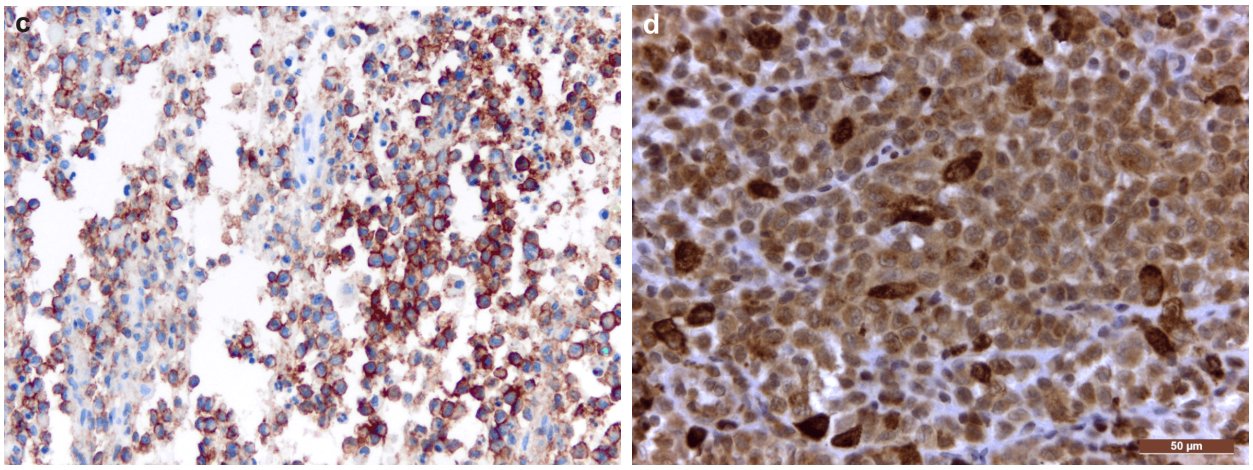

Figure 3 (continued) – ***(c) Immunohistochemistry of Langerhans cells showing intense CD1a expression (×200); (d) Immunohistochemistry of low (or variable expression) CD68 macrophage marker expression compared with the intensely CD68-positive infiltrated macrophages (×400). Brown staining of the nuclei and/or cytoplasm equals positive immunohistochemical expression.***

The patient underwent orbital surgery; subtotal curettage was performed followed by complete resolution of the tumor.

Discussion

As an entity, LCH was first described in 1893 by Alfred Hand Jr, but the Langerhans cell was previously defined in 1865 by the German physician Paul Langerhans [11, 18]. The different manifestations of the disease have been recognized step by step in following years, and in 1953, they have been organized by Lichtenstein & Jaffe under the name of "histiocytosis X" [1, 7, 18]. In 1987, by identifying Langerhans cells as the major cell type in the pathology of the disease, Nezelof *et al.* named the disease "Langerhans cell histiocytosis" or LCH [7, 18]. In the same year, during the *Workshop on Childhood Histiocytosis*, *The Writing Group* of the *Histiocyte Society* officially adopted the LCH term [1]. In 1990, the *LCH Study Group* divided the disease in two categories: single-system LCH or S-LCH, subdivided into unifocal (involving bones, skin and lymph nodes) and multifocal (involving bone and lymph nodes) and the multi-system LCH or MS-LCH (involving more than two organs), also subdivided into low-risk forms (where major organs, such as liver, lungs, spleen, bone marrow are not affected), and high-risk forms (where one or more of these organs are involved) [19]. For instance, a localized infiltrate of the orbit is considered as single-system, unifocal disorder with good prognosis; an infiltrate involving the orbit and other bones (including skull and lower limbs) is classified as a single-system, multifocal disease, with a medium long-term prognosis; an infiltrate involving bones, lungs and spleen belongs to the multi-system, high-risk group [11, 18, 19].

A pathological three-class system was introduced (class I – LCH; class II – non-LCH; class III – malignant histiocytic disorders) but later it was reorganized into: class 1 – dendritic cell-related disorders [7, 18, 19]; class 2 – macrophage-related disorders and class 3 – malignant disorders. According to this system, our case belongs to class 1 – dendritic cell-related disorders. From a clinical point of view, a recent staging system describes four groups: A – bone-only or bone and contiguous soft tissue involvement; B – skin or mucosa only or involvement of related superficial lymph nodes; C – soft tissue and viscera only; D – multi-system disease [14]. In 2008, the *World Health Organization* (WHO) recommended to differentiate LCH from Langerhans cell sarcoma, which is a more pleomorphic variant [8]. Our case, being a solitary LCH, confined to the orbit, belongs to the group A.

Orbital involvement by LCH most often represents a unifocal disease [20–22]. Localized LCH or orbital eosinophilic granuloma is defined in those cases where the disease is confined to the bones or lungs [23, 24]. The bones are the commonest site for LCH (especially the flat ones) and in 60–80% they are the only system involved [11]. Eosinophilic granuloma is the most common form of Langerhans cell histiocytosis and carries the best prognosis (>95%) [11]. The descriptions of this form, generally have been limited to single-system disease reports, either unifocal in singular cases or multifocal in small case series [13, 15, 16].

The approximate incidence of the disorder is of 5.4/100 000 individuals [11]. It is a pediatric disease, more common in children less then 15 years of age, with an estimated incidence of 0.2–2/100 000 children [11, 12]; infants between 1–3 years old are most affected [3, 17]. In Europe, several studies have shown a higher incidence of approximately 4–6% children per year, higher in children younger than one year old (9–15.3%) and lower in children older than 10 years old (0.7–2%) [18]. In adults, LCH diagnosis is usually made at a mean age of 35±14 years old, the peak ranging from 20 to 30 years of age [18] (as in our case).

Patients with orbital eosinophilic granuloma tend to be males (60–70% of all the cases) [11, 12] in their first or second decade (our case) (male/female ratio is 2:1) [11].

In boys, LCH is usually diagnosed at a later age than in girls, who in turn present more serious organ involvement [18]. Most studies give a higher preponderance to unifocal and single-system disease (our case) over multi-system disease [1, 11]. Small children, younger than 2–3 years old,

suffer more often from multi-system LCH, with a more unfavorable outcome (75% of cases) [11, 18].

There is no evidence for one factor playing a pivotal role in the pathogenesis of LCH, though several factors such as genetic disorders, malignancies (*e.g.*, retinoblastoma, most of glioma, medulloblastoma) or viral infections (*e.g.*, Epstein–Barr virus, cytomegalovirus, human herpes virus 6, seasonal and environmental influenza) have been implicated [2, 18].

As a result, LCH etiology is controversial; the two pathogenic pathways, neoplastic and reactive, are still under debate, being thoroughly investigated today in the idea of identifying new treatment possibilities [7, 19].

Even though the genetic etiology was not yet clearly established, the neoplastic nature of the disease is supported by several genetic anomalies (*i.e.*, loss of heterozygosity, chromosomal abnormalities or gene mutations such as v-Raf murine sarcoma viral oncogene homolog B (*BRAF*) *V600E* gene mutation found in 50–60% of cases), that may explain the clonal expansive nature of Langerhans cells. Although it has been reported, familial clustering is however very uncommon [2, 19].

The reactive nature theory in LCH implies particular immunological dysfunctions that can transform the precursor cells into pathological Langerhans cells; these atypical immunoreactions determine an uncontrolled cytokine synthesis (known as the "cytokine storm") induced by several factors (*e.g.*, inflammation, virus, trauma, etc.), that may also explain some clinical symptoms. Moreover, the severity of the disease is directly influenced by this immature aberrant immune system [18, 19]. The immunological phenomenon is based on paracrine and autocrine intercellular stimulation: Langerhans cells release several inflammatory chemokines (such as C-C receptors, C-X-C receptors, ligands) that recruit the circulating cells (*i.e.*, immature dendritic cells, T-lymphocytes, macrophages, eosinophils) with the release of a new wave of additional cytokines (*i.e.*, tumor necrosis factor-α, leukemia inhibitory factor, granulocyte macrophage colony-stimulating factor, transforming growth factor-β and numerous interleukins, such as IL-1, IL-3, IL-4, IL-5, IL-8, IL-10) [19]. Other hypothesis assumes that rather than the uncontrolled proliferation, a longer survival associated with the expansion of T-cells, determines the accumulation of Langerhans cells. There are also reports, where a minor trauma is the first presentation of orbital LCH [18]. History of trauma might be coincidental (due to the increased number of eye or head injuries in children) [25]; trauma might just be the trigger for immune system activation that will subsequently induce LCH (acute injury was correlated with myeloid differentiation primary response 88 (MyD88)-dependent inflammatory responses and extracellular signal-regulated kinases in the brain) [18, 26].

The clinical presentation of LCH is given by the location and the extent of the disease [7]. The lesions may be asymptomatic, pointed out by accidental imaging, or symptomatic, with perilesional pain, swelling and tenderness. Headache, a general feeling of discomfort, fever and leukocytosis also may appear [11]. Although adults are not excluded (as it happened in our case), isolated orbital infiltrates usually occur in children. Orbital involvement may appear as solitary lesion (as in our case) or bilateral sequential involvements [18]. However, other several presentations can be found in the ocular adnexa: eyelid, conjunctiva, choroid, optic chiasm or cavernous sinus [18]. As a first presenting symptom (our case), orbital disease is rare and its acute presentation with periorbital edema implies an inflammatory reaction and a differential diagnosis with dacryoadenitis [7]. The typical intraorbital setting is that of rapidly progressive proptosis (particularly seen in posterior orbit lesions) [27], but only in half of the patients (the destruction of the orbital walls may give orbital decompression). However, dislocation of the eye globe has also been reported [7]. This patient, a 21-year-old male, presented with right intraorbital expanding mass that subsequently developed into a swelling of the right superior eyelid; this is the typical form of the disorder, that usually begins as a slowly growing (over weeks to months) and expanding mass in the superolateral region of the orbit, with partial edema of the superior eyelid [27] and perioccular erythema [27]; it can be easily confused with periorbital cellulitis and a differential diagnosis is mandatory [7]. Ptosis, eyebrow pain and tenderness are not excluded if LCH is located in the anterior orbit [28–30]. This may be misinterpreted as an infection [10]. Sometimes, minimal exophthalmia or hemorrhages can be noted [1].

Visual changes or limitation of the eye movements may not be present (our case); anyway, due to eyelid ptosis, visual impairment may occur, with the development of amblyopia; furthermore, if extraocular muscles are attained, ocular movement may be impaired resulting in diplopia [10]. Dilated retinal veins and macular edema may also appear on eye fundus examination [10]. The intracranial extent of the disease may determine edema with secondary optic atrophy, without the mandatory involvement of the optic nerve and chiasm [5].

A destructive bone lesion is commonly seen in the superior or superotemporal orbit [31, 32]; in our case, the bone erosion destroyed the greater wing of the sphenoid bone, with direct communication between the orbit and the temporal fossa. Neurological and systemic examinations may be within normal limits (our case), in spite of the fact that central nervous system (CNS) sequelae appear in LCH; still, the available literature data does not indicate an increased risk in orbital unifocal cases [18, 33].

Although Langerhans cell histiocytosis rarely occurs in the orbit and in adults, similar to our case, it should be considered in the differential diagnosis of osteolytic and space-occupying mass of the orbit and ocular adnexa processes. In patients with primary orbital involvement, other lesions, such as inflammatory processes (osteomyelitis, periorbital cellulitis, osteomyelitis, acute dacryocystitis, hematoma, dermoid cyst, inflammatory pseudotumor), or proliferative ones (metastatic neuroblastoma, Ewing sarcoma, chloroma, lymphoma, rhabdomyosarcoma, CNS peripheral primitive neuroectodermal tumor, meningioma, neuroepithelioma, primary bone tumors, lymphoma or leukemia [1, 3, 18–21]) need to be excluded. Yet, the main histological differential diagnosis of LCH includes lesions with similar features as granulomas (*i.e.*, giant-cell reparative granuloma, cholesterol granuloma, Erdheim–Chester disease with foamy histiocytes), cysts

(hemorrhagic cyst, giant-cell aneurysm of bone) or tumors (giant-cell tumor, histiocytic sarcoma). These entities need to be differentiated from LCH by immunohistochemistry [1, 18, 34].

The confirmation of LCH diagnostic requires the assessment of a possible systemic involvement due to the multifocal or the multi-system forms of the disease [1]. A complete medical history and systemic work-up have to be performed in all cases, considering that orbital lesion may be part of a multi-system form [18].

Detailed blood tests (hematological and biochemical), chest, abdominal and skeletal imaging surveys should be performed [1] (as they were performed in our case).

Concerning the presence of bone erosion, this can be well localized using X-ray (revealing a round/oval, ill-defined bordered, punched out lesion) [1, 12] or cranial CT scan; the latter (as performed in our case) better confirms the cortical erosion and also the soft tissue involvement [14, 35]. It is an excellent technique in aiding biopsies and surgical planning [11].

The extent and precise delineation of the disorder (usually a heterogeneously contrast enhanced mass with erosion capability) [1] is more accurately revealed by magnetic resonance imaging (MRI) and positron-emission tomography (PET) scan imaging. Additionally, on scintigraphy, there is an increased or decreased lesion tracer uptake, depending on the histological frame [11]. Lately, these radiological techniques (mainly the combination of MRI/CT or PET scan/CT) seem to be the most sensitive tests for the diagnostic or the disease response to therapy [1].

Biopsies either from the therapeutic site curettage (in single orbital lesion) or adjacent soft tissues (in multi-focal or multi-system diseases with orbit involvement) are crucial [1]. LCH is histologically characterized by typical granulomas (eosinophilic [23, 24] – our case, xanthogranulomas [36], etc.) that are the hallmark of chronic inflammation. The cells from the infiltrate produce prostaglandins, responsible for the medullary bone resorption [11].

Histologically, LCH lesions show areas of large histiocytes with grooved nuclei that exhibit immuno-reactivity for CD1a and S100 protein (Langerhans cells), interspersed with multinucleate giant cells (osteoclast-like multinucleated giant cells) (as seen in our case), immature and indeterminate cells, interdigitating cells, classic macrophages, foamy histiocytes from older lesions, sometimes with intracytoplasmic Charcot–Leyden crystals and T-lymphocytes) [18], eosinophils, lymphocytes and plasma cells. In the cytoplasm of Langerhans cells, the Birbeck granules are pathognomonic and they are visible on transmission electron microscopy (TEM). Necrosis and hemorrhage can be also present [18]. Fibrotic scar may appear after the spontaneous healing of bone lesions [18]. Nuclear pleomorphism and mitoses have been occasionally observed, but they are not numerous. No correlation was found between the histological features and the disease severity [18].

On histopathological specimens, the diagnosis is favored by the predominant Langerhans cells infiltrate (they resemble more with macrophages rather than with typical skin dendritic cells [18]); the presence of accompanying cellular types is not mandatory [18, 19].

Originally, the *International Histiocyte Society* stated that a positive diagnosis requires positive staining for minimum two of the following: adenosine triphosphate, S100 protein antibody, α-mannosidase or peanut lectin [14, 18]. Yet, the combination between the positive immunostaining for S100 protein (Figure 3, a and b)/ CD45 neuronal markers with CD1a (Figure 3c)/CD207 [1], specific for Langerhans cells and not expressed by macrophages [18, 19], is frequently used in practice. CD68+ macrophages (Figure 3, c and d) may be also found, associated with hemophagocytic syndrome [18].

Still, the hallmarks of LCH diagnosis are the intra-cytoplasmic Birbeck granules, which are identified by TEM in 2–29% of the pathological Langerhans cells, in 50–70% of cases [18, 19]. Due to the fact that CD207 (langerin) seems to be correlated with the presence of the Birbeck granules, the recently found highly specific and sensitive monoclonal antibody against it (*e.g.*, clone DCGM4/122D5) becomes the golden standard [18].

In our case, the characteristic histological findings, S100 protein and CD1a positivity, supported by clinical features and the presence of bone erosion on CT were considered adequate for the diagnosis of LCH.

There are no definitive recommendations on how to best manage a case of orbital eosinophilic granuloma (due to the unknown pathogenesis of LCH, treatment management of the disease is still controversial [27] and it is largely based on disease extent and organ involvement). Since April 2009, treatment protocols regarding the latest strategies and clinical trials are provided by the *Histiocyte Society Evaluation and Treatment Guidelines*, as reference for medical evaluation of the patient [1]. Even though the therapeutic schemes always imply the triad: surgery, chemo- and radiotherapy, they are mostly designed for the multi-system form of the disease or the relapsing LCH. The protocol recommends systemic therapy in patients with orbit-associated lesions, such as skull base and temporal bone involvement or recalcitrant cases.

In case of orbital disorder, these schemes have to be adjusted [1, 10–12, 17]; no modality has been proven to be more effective than the other but lesions generally resolve after minimal intervention [1]. The orbital LCH carries the best prognosis, so treatment must remain as conservative as possible, even if recurrences and sequelae have still been reported after each therapeutic approach [1, 10, 23, 33]. Anyway, antibiotics and anti-inflammatory drugs or other symptomatic medication may be used as tools for differential diagnosis (*e.g.*, an inflammatory process such as orbital pericellulitis that would not respond to treatment) [23].

In unifocal LCH, the therapeutic regimen generally includes: biopsy, close clinical observation (in case of large lesions where resection might have functional or cosmetic side effects), and local surgical curettage; intra-lesional corticosteroid injections or low-dose radiotherapy may work for cases with painful lesions.

For solitary orbital lesions, incisional/excisional biopsy and curettage are firstly recommended (fine-needle aspiration may not offer sufficient material for the histological diagnosis) [11, 23, 27].

Complete surgical removal of the lesion is not even necessary. There are many reports of complete resolution

of an orbital eosinophilic granuloma (or other localized forms: lachrymal caruncle, eyelid) after biopsy and subtotal curettage alone [15, 16, 23, 34, 35]; even lesions with significant bone destruction and soft tissue involvement respond to this minimal intervention [10, 22, 23, 28]. The disruption of the pathological cascade due to changes in the microenvironment may favor this positive outcome [18, 27]. A close follow-up (with orbital MRI performed every year) is yet mandatory, recurrences being expected [18, 27].

Aggressive local strategies (*i.e.*, surgical resection, radiotherapy) or systemic chemotherapy could be considered as overtreatment, due to their possible systemic side effects or complications, and in most cases are not indicated (clinical trials are required to optimize their risk/benefit ratio [1, 18, 19]; chemotherapy and low-dose radiotherapy are generally required for extensive lesions in multifocal or multi-system forms [1, 14, 17, 23, 37]. Low-dose radiation may be given to induce remission in orbital histiocytosis, as an effective option in aggressive forms [1, 23]. The follow-up in the context of a multidisciplinary approach is necessary [5, 7, 14, 17, 37] within three years after the initial treatment; progression or recurrences of the disease being expected after 1–2 years in localized lesions [38] or even longer disease-free intervals (13–16 years). In multifocal forms of the disease, these ranges are halved (*i.e.*, 10 years after jaw involvement) [18, 22].

In the present case, subtotal curettage was performed, followed by complete resolution; an orbital MRI performed one year after surgical excision of the lesion showed no evidence of recurrence.

Conclusions

Despite its rarity, any case of a child or young adult (especially male) that presents an orbital involvement with osteolytic consequences may raise the suspicion of a Langerhans histiocytosis. The correlation between the particular histological features and S100 protein/CD1a positivity of Langerhans cells, the clinical findings and the CT images confirming the bone erosion are considered adequate criteria for the diagnosis of the disease. In case of eosinophilic granuloma, the treatment is conservative (biopsy and subtotal curettage) and carries the best prognosis, but a follow-up (orbital MRI performed every year for three years) is needed in order to prevent the recurrences.

Conflict of interests

None.

Consent

Written informed consent was obtained from the patient for the publication of images in Figure 1, a and b.

References

[1] Liang C, Liang Q, Du C, Zhang X, Guo S. Langerhans' cell histiocytosis of the temporal fossa: a case report. Oncol Lett, 2016, 11(4):2625–2628.

[2] Yoon JH, Park HJ, Park SY, Park BK. Langerhans cell histiocytosis in non-twin siblings. Pediatr Int, 2013, 55(3): e73–e76.

[3] Allen RC, Nerad JA. The little boy with an allergy that wouldn't go away. EyeNet Magazine, 2005, 9(6):41–42.

[4] Chu T, Jaffe R. The normal Langerhans cell and the LCH cell. Br J Cancer Suppl, 1994, 23:S4–S10.

[5] Glotzbecker MP, Carpentieri DF, Dormans JP. Langerhans cell histiocytosis: clinical presentation, pathogenesis, and treatment from the LCH Etiology Research Group at The Children's Hospital of Philadelphia. Univ Penn Orthop J, 2002, 15(1):67–73.

[6] Nezelof C, Basset F. Langerhans cell histiocytosis research. Past, present, and future. Hematol Oncol Clin North Am, 1998, 12(2):385–406.

[7] Bhanage AB, Katkar AD, Ghate PS. Langerhans cell histiocytosis with presentation as orbital disease. J Pediatr Neurosci, 2015, 10(2):162–165.

[8] Favara BE, Feller AC, Pauli M, Jaffe ES, Weiss LM, Arico M, Bucsky P, Egeler RM, Elinder G, Gadner H, Gresik M, Henter JI, Imashuku S, Janka-Schaub G, Jaffe R, Ladisch S, Nezelof C, Pritchard J. Contemporary classification of histiocytic disorders. The WHO Committee on Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. Med Pediatr Oncol, 1997, 29(3):157–166.

[9] Furuta S, Sakaki S, Hatakeyama T, Kumon Y, Nakamura K. Pediatric orbital eosinophilic granuloma with intra- and extracranial extension – case report. Neurol Med Chir (Tokyo), 1991, 31(9):590–592.

[10] Wirtschafter JD, Nesbit M, Anderson P, McClain K. Intralesional methylprednisolone for Langerhans' cell histiocytosis of the orbit and cranium. J Pediatr Ophthalmol Strabismus, 1987, 24(4):194–197.

[11] Sevillano C, Lázaro VM, Couselo JM, Freire J. [Orbital Langerhans cell histiocytosis: a multidisciplinary approach]. An Pediatr (Barc), 2010, 72(2):160–161.

[12] Zhou XD, Song GX, He YJ. [Clinical analysis of orbital histocytosis X]. Zhonghua Yan Ke Za Zhi, 2003, 39(11):673–677.

[13] Heuer HE. Eosinophilic granuloma of the orbit. Acta Ophthalmol (Copenh), 1972, 50(2):160–165.

[14] 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(3):137–140.

[15] Jakobiec FA, Trokel SL, Aron-Rosa D, Iwamoto T, Doyon D. Localized eosinophilic granuloma (Langerhans' cell histiocytosis) of the orbital frontal bone. Arch Ophthalmol, 1980, 98(10):1814–1820.

[16] 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(1):119–121.

[17] Bi L, Sun B, Lu Z, Shi Z, Wang D, Zhu Z. Langerhans cell histiocytosis with multisystem involvement in an infant: a case report. Exp Ther Med, 2015, 9(6):2137–2140.

[18] Herwig MC, Wojno T, Zhang Q, Grossniklaus HE. Langerhans cell histiocytosis of the orbit: five clinicopathologic cases and review of the literature. Surv Ophthalmol, 2013, 58(4):330–340.

[19] Ulivieri S, Oliveri G, Filosomi G. Solitary Langerhans cell histiocytosis orbital lesion: case report and review of the literature. Neurocirugia (Astur), 2008, 19(5):453–455.

[20] Glover AT, Grove AS Jr. Eosinophilic granuloma of the orbit with spontaneous healing. Ophthalmology, 1987, 94(8):1008–1012.

[21] Demirci H, Shields CL, Shields JA, Eagle RC Jr. Bilateral sequential orbital involvement by eosinophilic granuloma. Arch Ophthalmol, 2002, 120(7):978–979.

[22] 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.

[23] Wladis EJ, Tomaszewski JE, Gausas RE. Langerhans cell histiocytosis of the orbit 10 years after involvement at other sites. Ophthal Plast Reconstr Surg, 2008, 24(2):142–143.

[24] Petridis AN, Giannopoulos TL, Anastasiadou K, Sidiropoulou MS, Palladas P. Solitary Langerhans cell histiocytosis of the orbital wall. Eur J Radiol Extra, 2004, 51(3):95–97.

[25] Chang Y, Li B, Zhang X, Shent L, Jonas JB. Ocular trauma as the first presentation of Langerhans cell histiocytosis. Eye Sci, 2013, 28(4):204–207.

[26] Karki P, Hirano H, Yamahata H, Fujio S, Yonezawa H, Iida K, Bohara M, Oyoship T, Hanaya R, Arita K. Solitary cranial Langerhans cell histiocytosis: two case reports. Hiroshima J Med Sci, 2015, 64(4):59–63.

[27] Kiratli H, Tarlan B, Söylemezoglu F. Langerhans cell histiocytosis of the orbit. Eur J Ophthalmol, 2013, 23(4):578–583.
[28] Kramer TR, Noecker RJ, Miller JM, Clark LC. Langerhans cell histiocytosis with orbital involvement. Am J Ophthalmol, 1997, 124(6):814–824.
[29] Sarkar S, Singh M, Nag D, Dutta H, Banerjee A, Bhaduri G, Jha A. A case report of unifocal Langerhans' cell histiocytosis or eosinophilic granuloma. J Indian Med Assoc, 2007, 105(4): 218, 220.
[30] Schmitz L, Favara BE. Nosology and pathology of Langerhans cell histiocytosis. Hematol Oncol Clin North Am, 1998, 12(2): 221–246.
[31] Moore AT, Pritchard J, Taylor DS. Histiocytosis X: an ophthalmological review. Br J Ophthalmol, 1985, 69(1):7–14.
[32] Shetty SB, Mehta C. Langerhans cell histiocytosis of the orbit. Indian J Ophthalmol, 2001, 49(4):267–268.
[33] 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(1):28–34.
[34] Rajendram R, Rose G, Luthert P, Plowman P, Pearson A. Biopsy-confirmed spontaneous resolution of orbital Langerhans cell histiocytosis. Orbit, 2005, 24(1):39–41.
[35] Yi G, Yoon HK, Kim BK, Kim KA, Choo IW. CT findings of orbital Langerhans cell histiocytosis. J Korean Radiol Soc, 2000, 42(5):841–846.
[36] Tamir I, Davir R, Fellig Y, Weintraub M, Constantini S, Spektor S. Solitary juvenile xanthogranuloma mimicking intracranial tumor in children. J Clin Neurosci, 2013, 20(1):183–188.
[37] Nicollas R, Rome A, Belaïch H, Roman S, Volk M, Gentet JC, Michel G, Triglia JM. Head and neck manifestation and prognosis of Langerhans' cell histiocytosis in children. Int J Pediatr Otorhinolaryngol, 2010, 74(6):669–673.
[38] Vosoghi H, Rodriguez-Galindo C, Wilson MW. Orbital involvement in Langerhans cell histiocytosis. Ophthal Plast Reconstr Surg, 2009, 25(6):430–433.

Corresponding author
Eleonora Dronca, MD, PhD, Department of Molecular Sciences, "Iuliu Haţieganu" University of Medicine and Pharmacy, 6 Pasteur Street, 400349 Cluj-Napoca, Romania; Phone +40740–198 218, e-mail: eleonora.dronca@umfcluj.ro

Received: June 20, 2017

Accepted: February 8, 2018