Ophthalmic Manifestations in Langerhans Cell Histiocytosis

Jaime Levy MD[1], Tova Monos MD[1], Joseph Kapelushnik MD[2], Esther Maor MD[3], Michael Nash MD[4] and Tova Lifshitz MD[1]

Departments of [1]Ophthalmology, [2]Pediatric Hematology, [3]Pathology and [4]Otolaryngology-Head & Neck Surgery, Soroka Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

Key words: Langerhans cell histiocytosis, ophthalmic manifestations

Abstract

Histiocytosis of childhood is characterized by localized or generalized proliferation of cells of the mononuclear phagocyte system and the dendritic cell system. In patients with Langerhans cell histiocytosis, the orbit is the most involved site encountered in ophthalmic practice, usually as a lytic lesion in the zygomaticofrontal suture. Patients usually present with acute or chronic periorbital swelling. Electron microscopic findings of Birbeck granules and positive staining for CD1 antigenic determinant confirm the diagnosis.

IMAJ 2004;6:553–555

Histiocytosis of childhood comprises a group of disorders characterized by localized or generalized proliferation of cells of the mononuclear phagocyte system and the dendritic cell system. Lichtenstein in 1953 [1] proposed the term histiocytosis X to include three related disorders: eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease, which he believed were different clinical expressions of a single nosologic entity. Eosinophilic granuloma was described as histiocytic uni- or multi-focal mass lesions that generally originate in bone sites. Hand-Schüller-Christian disease, first described as the triad of exophthalmos, bony defects of the skull, and diabetes insipidus, was later applied to the chronic disseminated form of histiocytosis X involving both bone and soft tissues [2]. Letterer-Siwe disease was initially described as widespread soft tissue and visceral involvement with or without bone lesions with an acute or sub-acute and sometimes fatal course.

Recently, the Histiocyte Society redefined the classification of histiocytosis of childhood [3]. Class I includes the Langerhans cell histiocytosis. Class II includes histiocytosis of mononuclear phagocytes other than LCH, hemophagocytic lymphohistiocytosis (familial and reactive), sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease), juvenile xanthogranuloma, and reticulohistiocytoma. Finally, Class III includes the malignant histiocytic disorders such as acute monocytic leukemia (FAB M5), malignant histiocytosis, and true histiocytic lymphoma. The Histiocyte Society also established the criteria required for a definite diagnosis of LCH: namely, light microscopy morphologic characteristics plus Birbeck granules in the lesional cell seen on electron microscopy and/or staining positive for CD1a antigen on the lesional cell. Patients with LCH tend to fall into two particular groups: those who have disease limited to the bone or soft tissue, or both, and whose clinical course is relatively benign; and those who present with very diffuse disease that progresses despite multiple therapeutic interventions [4,5]. These groups can be distinguished at diagnosis on the basis of organ involvement or dysfunction. In order to standardize the classification of this disorder, a pathologic staging [6] has also been proposed, which is different from the clinical staging system. Basically, LCH is divided into Group A (bone only or bone and or contiguous soft tissue involvement), Group B (skin and/or other squamous mucous membranes only or with involvement of related superficial lymph nodes), Group C (soft tissue and viscera only), and Group D (multi-system disease). We review here the ophthalmic manifestations of the disease.

LCH = Langerhans cell histiocytosis

Clinical manifestations

In LCH, the orbit is by far the most involved site encountered in ophthalmic practice. The overall incidence of orbital involvement in patients with LCH in larger series ranges from 1% to 20% [7,8]. In a large series of more than 645 orbital biopsies [2], histiocytic and related lesions represented less than 1% of the orbital biopsies. In addition, in a series of 241 orbital biopsies taken from patients under the age of 20 years, only three cases of histiocytosis were found [9].

The orbit is the most involved site in ophthalmic practice in patients with Langerhans cell histiocytosis

Orbital involvement is almost invariably associated with a lytic lesion of the orbital wall, and it is usually characterized by osteolytic bone lesions with sclerotic margins. Involvement of the zygomaticofrontal suture is thought to be highly characteristic [Figure 1A], but many of the reported lesions have not been in this site [3,4]. The typical presentation is that of a slowly growing upper palpebral swelling over a period of weeks to months, at the temporal aspect, sometimes with erythema, and fullness to palpation [Figure 1B]. It can sometimes be confused with periorbital cellulitis. Acute presentation of periorbital swelling caused by LGH is rare [10–12], and is usually due to the growth of the lesion through the periorbita, inducing an inflammatory response, suggesting a dacryoadenitis clinically, and it is often

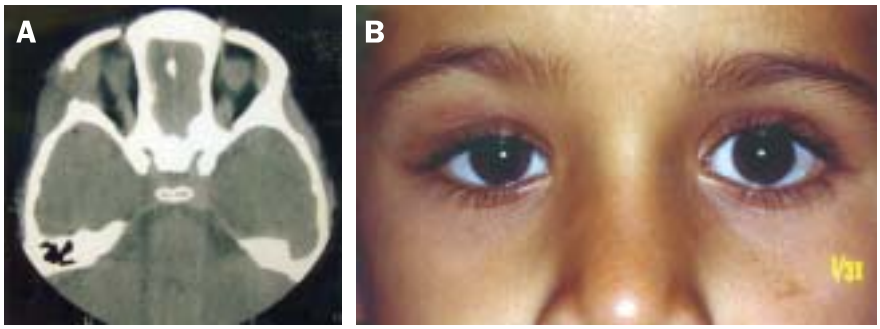

Figure 1. Five year old girl with Langerhans' cell histiocytosis. **[A]** Axial computed tomography scan showing a destructive soft tissue mass in the supero-lateral aspect of the right orbit, which eroded the fronto-zygomatic suture. **[B]** External appearance of the same patient showing minimal erythema and swelling of right upper lid.

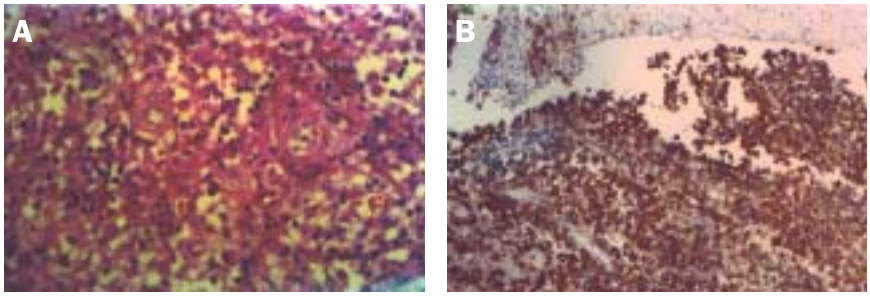

Figure 2. [A] Hematoxilin-eosin preparation showing Langerhans' cells admixed with eosinophils. **[B]** Immunohistochemistry on frozen tissue, demonstrating positive staining (brown color) for CD1A.

preceded by nasal congestion or epistaxis. Other far less frequent sites of orbital involvement sites are the sphenoid bone (three cases) and the ethmoid bone (described in only one case) [10]. Orbital involvement is rare in the acute disseminated form of histiocytosis X [8,11], and is usually seen in Groups A and B of the pathologic staging classification.

In a large series of pediatric orbital tumors [13], histiocytosis X represented 7% of 257 cases of proptosis seen in children under the age of 15 years. This relatively high figure is probably due to the fact that the series is from a tertiary referral center with a pediatric oncology unit. It should be remembered that LCH is an uncommon disease and its contribution to orbital disease in the general population is low, accounting for less than 1% or orbital tumefactions in most series [11]. Usually only half of the patients with orbital involvement developed proptosis [14]. If proptosis is severe it can cause globe luxation [15]. There may be radiologic evidence of orbital involvement without any accompanying clinical signs, but proptosis is almost always associated with a lytic lesion of the orbital wall [8,14]. Moore et al. [11], in a large series of 76 children with histiocytosis X, did not find any case of orbital involvement in patients whose disease was confined to the soft tissue, suggesting that in histiocytosis X the orbital lesion usually arises in bone. In the very rare cases of disease confined to orbital soft tissues without bone involvement, it is important to rule out other lesions that may contain eosinophils, such as granulocytic sarcoma and pediatric orbital pseudotumor [16,17].

In rare cases, usually with the chronic disseminated form of the disease, neuro-ophthamic complications may occur. Optic neuropathy and cranial nerve palsies are rare [18], as the orbital mass is usually extraconal, and destruction of the orbital walls may result in orbital decompression. However, optic neuropathy with third, fourth, and sixth-nerve palsies have been described [19]. Intracranial histiocytosis may result in papilledema and secondary optic atrophy, and also in involvement of the intraorbital optic nerve and chiasm. Ptosis and seventh-nerve palsy [11], and cavernous sinus syndrome [19] have also been described.

Intraocular involvement is very rare, and its occurrence is usually seen in infants with the sub-acute disseminated form. It consists of infiltration of intraocular structures, especially the uveal tract, with histiocytes. This may be an incidental finding at necropsy, but some patients will present with ocular abnormalities during their acute illness. These include uveitis, choroidal infiltrates, retinal detachment, spontaneous hyphema, secondary open-angle glaucoma, corneal ulcers and posterior scleritis [11].

Diagnosis

The diagnosis of Langerhans cell histiocytosis is ultimately confirmed by histopathologic examination of biopsy specimens of involved tissues. In children with orbital involvement as part of systemic disease, it is usually easier to take a biopsy specimen from another site such as the scalp or a peripheral bony lesion. The Histiocytosis Society recently defined objective criteria for diagnosing LCH, as we mentioned before [3]. A presumptive diagnosis can be made with a hematoxylin and eosin-stained specimen, showing large histiocytes (abnormal Langerhans cells) [Figure 2A]. A designated diagnosis needs light microscopy features plus two or more supplemental positive stains for adenosine triphosphatase, S100 protein, alpha-D-mannosidase, and/or peanut lectin. Finally, a definite diagnosis requires the light morphologic characteristics plus positive staining for CD1a antigen on the lesional cell [Figure 2B], and Birbeck granules in the lesional cell when examined with electron microscopy.

Acute or chronic periorbital swelling and a lytic lesion in the zygomaticofrontal suture are the most characteristic clinical features

New cases of LCH presenting to the ophthalmologist must be referred to a pediatric oncologist. The systemic evaluation recommended includes hemoglobin and/or hematocrit, white blood cell count and differential count, platelet count, liver function tests, serum (glutamic-oxoalacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase), bilirubin, total proteins, albumin, coagulation studies (prothrombine time, partial thrombo-

plastin time, fibrinogen), chest radiograph (postero-anterior and lateral), skeletal radiographic survey, and urine osmolality measurement after overnight water deprivation. The distinction between multi-system and single-system disease is important because proper prognosis and management depend on this initial assessment [20].

Treatment of orbital lesions

The therapy for LCH is still controversial because of the unpredictability of the outcome and the possibility of spontaneous healing [10]. The various treatment options include observation, surgical curettage, local injection of corticosteroids, low dose radiotherapy, high dose systemic corticosteroids, chemotherapy, and for more recalcitrant cases bone marrow transplantation and antibody therapy.

Many cases of LCH have been managed with close observation or watchful waiting [21]. In patients with a single orbital bony lesion, biopsy and curettage may be followed by spontaneous resolution [11]. However, if there is a marked proptosis, a cosmetically unacceptable lesion of the orbital wall, or evidence of optic nerve involvement, a short course of systemic steroids or radiotherapy may be used in an attempt to induce remission. No definite criteria have been established regarding when radiation should be used in the treatment of the orbital lesions. A short course (150 centigrays/day during 4 days) can be attempted for lesions inaccessible to intralesional steroid treatment or when there is evidence of optic nerve involvement [22]. However, excessive radiation can cause cataracts and damage to the optic nerve or globe [23], or induce post-irradiation tumors [24]. When there is orbital involvement as part of multi-system disease, systemic treatment with corticosteroids with chemotherapy – usually vinblastine – has been shown to be effective [25]. Although not effective for bone restoration, the corticosteroid-chemotherapy regimen will reduce the size of the mass. This treatment should be carried out under the supervision of a pediatric oncologist.

Prognosis

The prognosis in LCH depends upon several factors: a) response to initial therapy; b) age at diagnosis (in children less than 2 years old at diagnosis, the 5 year mortality rate is about 55–60%); c) the number of organs involved at diagnosis; d) the presence of organ dysfunction at diagnosis (if present the 5 year mortality reported is 66%); and e) natural history with treatment (cases with no disease progression over 6–12 months carry the best prognosis with no mortality reported, whereas children who progress to develop organ dysfunction during the course of the disease usually die within 5 years).

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Correspondence: Dr. J. Levy, Dept. of Ophthalmology, Soroka Medical Center, P.O. Box 151, Beer Sheva 84101, Israel.
Phone: (972-8) 640-0379
Fax: (972-8) 640-3927
email: ljaime@bgumail.bgu.ac.il