

# Langerhans Cell Histiocytosis Presenting as Acute Eyelid Edema

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## ABSTRACT

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Langerhans cell histiocytosis (LCH) is a group of disorders involving an abnormal monoclonal proliferation of Langerhans cells. Children and young adults are most commonly affected. We present a case of a 10-year-old male who presented with acute right upper eyelid edema and ecchymosis occurring over a 2-day period. CT of the orbits demonstrated a soft tissue mass in the right superior orbit causing a lytic bone lesion in the orbital roof allowing for tumor extension into the anterior cranial fossa. Histopathologic examination of a lesion biopsy revealed Birbeck granules, confirming a diagnosis of LCH. The patient received intralesional steroids but further osseous destruction was observed. Systemic therapies were initiated with adequate response and improvement of the bony defects. We are presenting this case because of its unusual presentation as acute onset eyelid edema with rapid progression, in the absence of trauma.

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## INTRODUCTION

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Langerhans cell histiocytosis is a group of proliferative disorders involving pathologic Langerhans cells (PLC), with each disorder demonstrating its own unique clinical traits while sharing a common histologic appearance. Previously named Histiocytosis X by Dr. Louis Lichtenstein in 1953, LCH encompasses the entities eosinophilic granuloma of bone (EGB), Hand-Schüller-Christian disease (HSC), and Letterer-Siwe disease (LSD). EGB is the most common form of LCH and represents the milder form of this disease. It is characterized by unifocal bone involvement most commonly affecting the skull bones and generally follows a benign, self-limited course requiring minimal intervention. HSC is the intermediate form, characterized by multifocal bone lesions. LSD is the acute disseminated LCH affecting multiple organ systems. It is the most severe form of LCH. It typically affects children less than 2 years of age and has the poorest prognosis. The older eponyms have largely been replaced by more clinically descriptive classifications: unifocal, multifocal, and systemic LCH.

Reported incidence of LCH is varied, ranging from 2.24-8.9 cases per 1,000,000 children. Recent studies found incidence to be 4.12-4.6 cases per 1,000,000 children younger than 14 years of age.<sup>1</sup> Peak incidence occurs between ages 1 to 3.<sup>2</sup> The disease shows a predilection for males, in some reports as high as 2:1. The mortality rate of LCH has been reported as high as 50% in cases having involvement of risk organs, and 20% in those without. By some accounts, there is a 50% 5-year survival rate in children under 2 years of age despite aggressive chemotherapy.

Langerhans cells function primarily to process foreign antigens and present them to T-cells. Whereas normal Langerhans cells are found primarily in the skin, lymph nodes, lungs, and thymus, PLCs may also be found in the bones, bone marrow, spleen, liver, central nervous system and gastrointestinal tract.<sup>3</sup> Although an etiology has yet to be determined, it has been proposed that an immune insult, either transient or persistent, may provide the stimulus for PLCs to proliferate within the frontal bone, the most skull bone affected by LCH.<sup>4</sup> PLCs have been shown to be the only cells within LCH biopsies that produce interleukin-1 (IL-1), an osteolytic cytokine.<sup>5</sup> Lytic lesions resulting from IL-1-induced bone resorption permit tumor extension into the orbit, temporal fossa,

anterior cranial fossa, and forehead. Osteolysis may also result from PLC elaboration of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>).

The gold standard for definitive diagnosis of LCH is the presence of Birbeck granules demonstrated by electron microscopy. These granules, located within the cytoplasm of pathologic Langerhans cells, are characteristic rod-shaped organelles with an appearance often described as a tennis racquet. Presumptive diagnosis of LCH can be made based on positive staining for S100 protein and CD1a+ antigen.

Orbital LCH typically manifests as a palpebral mass with slow growth over a period of weeks to months, but in rare instances may present as acute proptosis, globe displacement, and eyelid swelling. The differential diagnosis must include other processes capable of causing rapidly progressive eyelid and facial swelling, such as rhabdomyosarcoma, metastatic neuroblastoma, osteogenic sarcoma, and Ewing sarcoma.<sup>6</sup> The differential diagnosis also includes orbital cellulitis, orbital pseudotumor, sarcoidosis, and Wegener's granulomatosis.



Figure 1. External photograph depicting edema, ecchymosis, and ptosis of the right upper eyelid.

## CASE PRESENTATION

A healthy 10-year-old Caucasian male presented for evaluation of an apparent injury to his right eye. He complained of his right upper eyelid being "black and blue" and of his lid slowly drooping, all occurring 2 days earlier. He also noted a constant dull pain with occasional sharp pains. Pain was increased when patient laid on his right side. He recently participated in a soccer tournament but does not recall any specific trauma to his eyes, although he did contact the soccer ball with his head on several occasions. He denied fever and chills.

Visual acuity without correction was 20/20 OD and 20/20-2 OS. Pupillary examination revealed equal and reactive pupils bilaterally without evidence of an afferent papillary defect. Motility examination demonstrated orthophoria and full extraocular movements OU. Confrontational visual fields were constricted superiorly OD secondary to ptosis, and full OS. No proptosis was noted. Eyelid ecchymosis was present in the right upper eyelid with tenderness to palpation (Figure 1). Conjunctiva, sclera, cornea, anterior chamber, iris, and lens were normal OU. Fundus examination revealed clear media OU, cup-to-disc ratio of 0.2 OU, mildly tortuous vessels OU, and normal macula and periphery OU.

A CT scan of the orbits revealed a 2.1 x 1.8 x 1.3cm soft tissue mass in the right superior orbit emanating primarily from the marrow space of the frontal bone (Figure 2). This

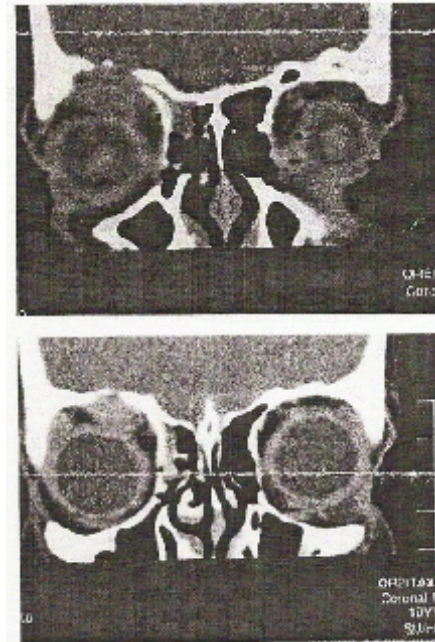


Figure 2. CT of the orbits depicting a tumor in the superior right orbit and a lytic lesion of right orbital roof with tumor extension into frontal sinus and anterior cranial fossa.

mass was causing displacement the globe inferiorly and destruction of the superior orbital rim with extension into the frontal sinus. The anterior cranial floor was also destroyed with apparent tumor extension into the anterior cranial fossa.

The patient was referred to Jules Stein Eye Institute for further evaluation. His right eye at that time demonstrated a -2 upgaze deficit, a -2 right gaze deficit, and a -2 up-and-right gaze deficit. Other pertinent findings OD included 2/4 periorbital edema, 3/4 periorbital ecchymosis, MRD<sub>1</sub> of 2.5mm (5.0mm OS), 3mm inferior displacement of the globe, increased firmness to retropulsion, and positive orbital pulsations.

The lesion was subsequently biopsied and debulked to the level of the dura through a lateral orbitotomy. Microscopic examination of the tissue revealed sheets of lobated histiocytic cells with clefts within nuclei scattered among clusters of eosinophils. Scattered multinucleated giant cells were also present. Immunohistochemistry results showed high concentration of antibodies to S100 protein within the histiocytic cells. Electron microscopy identified Birbeck granules, confirming the diagnosis of LCH. Two weeks later, the patient received a local injection of triamcinolone acetate, with a plan for a three month course of once monthly injections. Marked improvement in the periorbital edema was noted one week after the initial injection (Figure 3). A repeat CT scan performed one week prior to the next followup appointment showed significant reduction in the soft tissue component of the tumor, but the osseous component showed significant enlargement with further bony destruction (Figure 4).

One week later, the patient was started on systemic treatment. The patient returned for a 4-month followup visit and at that time was without complaint. He was still receiving chemotherapy and was tolerating the treatment well. On examination, visual acuity was 20/20 OU, motility was full OU, and the right upper eyelid ptosis had resolved. Review of recent imaging studies showed improvement in the bony defects present in the right orbit. Our patient completed chemotherapy at Jules Stein Eye Institute. He returned to our clinic 3 years after his initial presentation and at that time demonstrated full ocular motility and had no subjective complaints. Radiographic studies performed in the interim showed no recurrence of disease.

## DISCUSSION

Langerhans cell histiocytosis is a neoplasm that occurs very rarely in the orbit. The disease accounts for less than

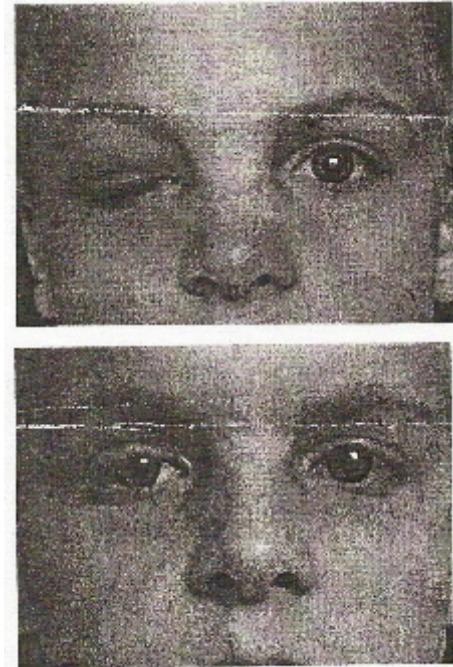


Figure 3. External photographs depicting right upper eyelid edema and ptosis before initial triamcinolone injection (top) and 1 week after injection (bottom).

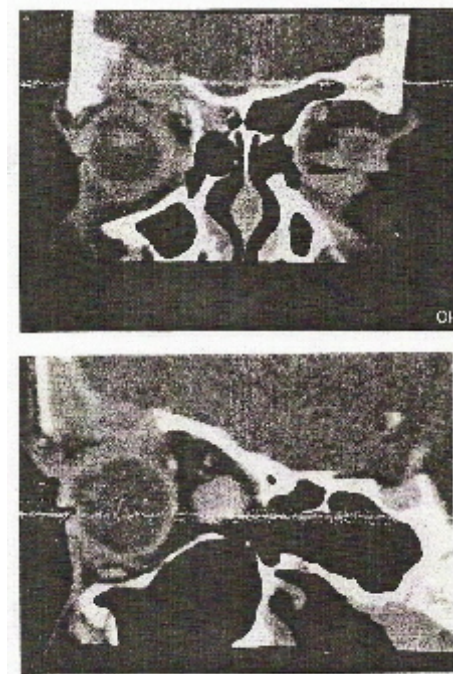


Figure 4. CT of the orbits depicting further bony destruction of right superior orbit with reduction of soft tissue tumor component.

1% of orbital tumors. Orbital involvement may be found in 1% to 20% of LCH cases. It is also rare for LCH to present as acute periorbital swelling, particularly in the absence of trauma as was the case with our patient.<sup>7</sup> The literature has described cases of orbital LCH that presented as acute periorbital swelling occurring within days of direct trauma to the affected eye. We acknowledge that the patient's act of contacting the soccer ball with the crown of his head could have contributed to the initial clinical presentation, although direct contact or injury to the right eye or eyelid was denied. Our preliminary differential diagnosis included rhabdomyosarcoma, inflammatory processes, or orbital hematoma. LCH was not considered initially.

Corticosteroids have been shown to inhibit IL-1-induced bone resorption and PGE<sub>2</sub> production. Both of these cytokines are overexpressed by PLCs and have been strongly implicated in causing the lytic bone lesions associated with LCH that allow tumor advancement into the cranium.<sup>5</sup> Hence, the progression of the bony destruction after intralesional injection of corticosteroids was not anticipated. The examiners could have misinterpreted the drastic improvement in the periorbital edema and ptosis as treatment success, but instead appropriately performed repeat radiographic studies. The second CT scan allowed for identification of the growing destruction within the orbital bones. Because the osseous component of the tumor continued to worsen, treatment was escalated to systemic modalities. This scenario highlights the importance of serial imaging in disease stratification and subsequent evaluation of a patient's response to treatment, even.

According to the Third International Study for Langerhans Cell Histiocytosis (LCH-III) conducted by the Histiocytosis Society, lesions involving facial bones or the anterior or middle cranial fossa are defined as CNS-risk lesions. These lesions carry a risk for meningeal involvement and a 3-fold risk for developing permanent central nervous system disease.<sup>8</sup> CNS involvement may be found in up to 25% of patients, with the most common sequelae being diabetes insipidus (DI) and anterior pituitary dysfunction.<sup>9</sup> DI results from decreased antidiuretic hormone secretion, while anterior pituitary dysfunction most commonly manifests as a decrease in growth hormone secretion.<sup>10</sup> Our patient has a CNS-risk lesion due to tumor extension into the anterior cranial fossa. Recurrence may occur and is most commonly encountered within 2 years of the initial diagnosis, but has been reported as much as 16 years after initial diagnosis.<sup>11</sup> Because of the potential for distant recurrence, long-term followup and evaluation of patients with this disease is mandatory and should include serial imaging.

LCH-III is a multi-armed pilot study with a primary objective to reduce morbidity associated with CNS-risk lesions, including the rate of recurrence/reactivation and development of permanent consequences. For these lesions, the LCH-III treatment protocol recommends initial treatment with continuous oral prednisone 40mg/m<sup>2</sup> daily in 3 doses for 4 weeks, followed by a 2-week taper, and vinblastine 6mg/m<sup>2</sup> intravenous bolus on day 1 of weeks 1-6. Initial treatment is repeated once for only those patients in whom disease progression is noted. Continuation treatment is then initiated in patients with no active disease after 6 weeks of therapy or patients with improving active disease after 12 weeks of therapy. Continuation treatment consists of oral prednisone 40mg/m<sup>2</sup> in 3 doses on days 1-5 every 3 weeks, and vinblastine 6mg/m<sup>2</sup> intravenous bolus on day 1 every 3 weeks. Treatment continues for a period of 6 months. This regimen is consistent with the treatment of multifocal bone disease, as CNS-risk lesions cannot be regarded as single system disease and should not be treated as such because of the potential for permanent neuroendocrine dysfunction.

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## CONCLUSION

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The usual presentation of Langerhans cell histiocytosis is that of a child or young adult with a superotemporal or lateral orbital mass exhibiting slow growth over a period of weeks to months.

Our patient experienced acute periorbital swelling with rapid progression, which is rare. Imaging with CT and MRI are paramount in determining the presence of an orbital neoplasm and the extent of periocular involvement, but definitive diagnosis of LCH cannot be made without histologic examination of the tumor. Given the marked variability in disease severity and the potentially high mortality rate associated with systemic disease, LCH must always be included in the differential diagnosis when evaluating a patient with acute, rapidly progressive eyelid edema, proptosis, or globe displacement.

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What constitutes local therapy? Low-dose radiation, intralesional corticosteroids (known to inhibit IL-1-induced bone resorption and production of prostaglandin E<sub>2</sub>)

Stem cell precursors of Langerhans cells reside in active bone marrow and differentiate under cytokine influence.

Acute presentation of periorbital swelling is rare and usually due to growth of the lesion through the periorbita, including an inflammatory response that is often preceded by nasal congestion and epistaxis

Many of the entities in the differential have been known to present acutely and may result in severe sequelae if not identified and treated in a timely manner.

Recurrence has been reported as much as 16 years after initial diagnosis, mandating long-term followup and evaluation of patients with this disease.

Langerhans cell histiocytosis, formerly known as Histiocytosis X, encompasses a group of disorders involving an abnormal proliferation of pathologic Langerhans cells (PLC) and overproduction of inflammatory cytokines.<sup>1</sup> Three clinical entities have been identified: eosinophilic granuloma of bone, Hand-Schüller-Christian disease, and Letterer-Siwe disease. These entities represent a spectrum of disease, from unifocal disease that often follows a benign, self-limited course, to acute disseminated disease that may be vision and life threatening.<sup>2</sup>

Langerhans cells are normally found in the epidermis and function primarily to process foreign antigens and present them to T-cells. The cytoplasm of PLCs contains Birbeck granules, characteristic rod-shaped organelles with an appearance often described as a tennis racket. Demonstration of these granules by electron microscopy allows for definitive diagnosis of LCH.<sup>3</sup> It has been proposed that an immune insult, transient or persistent, may provide the stimulus for PLCs to proliferate within the frontal bone.<sup>4</sup> PLCs have been shown to be the only cells within LCH biopsies that produce interleukin-1 (IL-1), an osteolytic cytokine.<sup>5</sup> Lytic lesions resulting from IL-1-induced bone resorption permit tumor extension into the orbit, temporal fossa, anterior cranial fossa, and forehead.