

Case Report

Langerhans cell histiocytosis in an 18-month-old child presenting as periorbital cellulitis



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Abstract

Langerhans cell histiocytosis (LCH) is a rare multi-system disease. It presents infrequently as a childhood orbital tumor, and can mimic more common inflammatory orbital disease processes. We report the clinical, histopathological, and electron microscopic findings of orbital LCH in an 18-month-old child, along with a review of the recent literature regarding molecular pathogenetic analysis of LCH. The child presented with a two-week history of progressive left periorbital edema and redness. He was initially diagnosed and treated empirically for bacterial periorbital cellulitis, but subsequently underwent ophthalmological consultation after he failed to improve. Histopathological examination of an orbital biopsy specimen revealed numerous Langerhans-type cells, which stain positive for CD1A and CD207 (langerin). Electron microscopic examination demonstrated characteristic Birbeck granules within the Langerhans-type cells. Three year follow-up did not demonstrate recurrence or disease progression.

Keywords: Langerhans cell histiocytosis, Langerin, Periorbital cellulitis, Birbeck granules, LCH-III protocol

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<https://doi.org/10.1016/j.sjopt.2018.02.006>

Introduction

Langerhans cell histiocytosis (LCH) is a rare multi-system disease with a diverse clinical presentation. It is infrequently encountered in clinical practice, with an annual incidence of 3–5 cases per million children.¹ Orbital involvement in LCH is relatively uncommon, ranging from 1 to 20% of LCH cases.² The diagnosis is only confirmed histologically by tissue biopsy with positive staining of specimens with CD1A and CD207 (langerin), as well as with identification of characteristic Birbeck granules with electron microscopy (EM). LCH was previously thought to be derived from Langerhans cells, which are specialized dendritic cells of the skin and mucosa;³ however, recent studies using molecular and genetic analysis have

revealed that Langerhans cells of the skin may not actually be the cell of origin.⁴ Localized LCH lesions are rather composed of myeloid progenitor cells from the bone marrow that share the same antigens (CD1a and langerin).⁴ Genetic studies identifying oncogenic mutations of BRAF and MAP2K1 in LCH have supported a shift in the debate toward LCH as a neoplasm rather than a reactive process.^{5–7} LCH most commonly affects Caucasian males, with the onset in the first or second decade.⁵ Ophthalmic involvement of LCH can mimic other diseases of the orbit, particularly infectious periorbital or orbital cellulitis. Eyelid edema, proptosis, ptosis, optic atrophy, and papilledema may be noted in both conditions.² We report a case of LCH in a child who presented initially as periorbital cellulitis.

Received 27 November 2017; received in revised form 7 February 2018; accepted 8 February 2018; available online 16 February 2018.

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Case report

An 18-month-old previously healthy Liberian boy presented to our pediatric emergency department with a two-week history of progressive left periorbital edema and redness. The lesion began as a small red bump on the left upper eyelid, presumed to be secondary to an insect bite, but it expanded rapidly to involve the left forehead over several days (Fig. 1A). At the same time, the patient's parents noted that the boy had reduced energy, appetite, and a low-grade fever. A clinical diagnosis of periorbital cellulitis was made, and the child was treated as an outpatient with empiric oral antibiotic therapy (cefprozil). The patient's left eyelid swelling worsened over the following 48 h and he was admitted for intravenous antibiotic therapy (ceftriazone, vancomycin, and metronidazole). Ophthalmic consultation disclosed a normal right eye, but a non-tender, erythematous swelling of the left upper eyelid with prominent left proptosis and deficits in left eye supraduction and abduction. An orbital computed tomography (CT) scan revealed a lytic lesion centered in the superolateral left frontal bone (Fig. 1B). Subsequent magnetic resonance imaging (MRI) demonstrated a well-circumscribed heterogeneous mass with adjacent destruction of the left frontal bone, associated with enhancement of the surrounding dura (Fig. 1C). Blood work revealed elevated lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), but the remainder of the systemic workup; including blood cultures, chest X-ray, skeletal survey, urine osmolality, abdominal ultrasound, and CT of the abdomen and thorax, were all negative. An incisional biopsy via an extended lid crease anterior orbitotomy yielded fragments of a homogenous, reddish-brown, friable mass.

Histopathological examination disclosed numerous Langerhans-type cells with indented nuclei and abundant cytoplasm within a densely packed background of numerous eosinophils, lymphocytes, plasma cells, and polymorphonuclear leukocytes (Fig. 2A and B). Immunohistochemical stains were strongly positive for CD1A (Fig. 2C), a marker for T-cells and dendritic cells, and CD207 (langerin) (Fig. 2D), a marker for Birbeck granules, which together identified the presence of Langerhans-type cells. The lesion also stained positive for S100, CD68, and CD163 and stained negative for CD99 and neuron-specific enolase (NSE). Electron microscopic examination demonstrated characteristic Birbeck granules (Fig. 3A and B).

The patient was treated according to the LCH-III protocol, which included 3 phases of prednisone and vinblastine, followed by one year of maintenance therapy with 6-mercaptopurine and methotrexate.⁸ Seven months after initiating treatment, repeat MRI revealed almost complete resolution of the mass (Fig. 1D). In addition, the clinical appearance of the lesion was markedly reduced at 11 months post-operatively (Fig. 1E). Serial follow-up ophthalmologic examinations for three years after the diagnosis were unremarkable with no disease recurrence.

Discussion

Langerhans cell histiocytosis (LCH) encompasses a wide spectrum of clinical presentations, and has been termed several names pending the presenting findings including eosinophilic granuloma, Hand-Schuller-Christian disease, Letterer-Siwe disease, and histiocytosis X.¹ Eosinophilic granuloma is a slowly progressive disease characterized by proliferation of Langerhans type cells primarily in bones.⁵

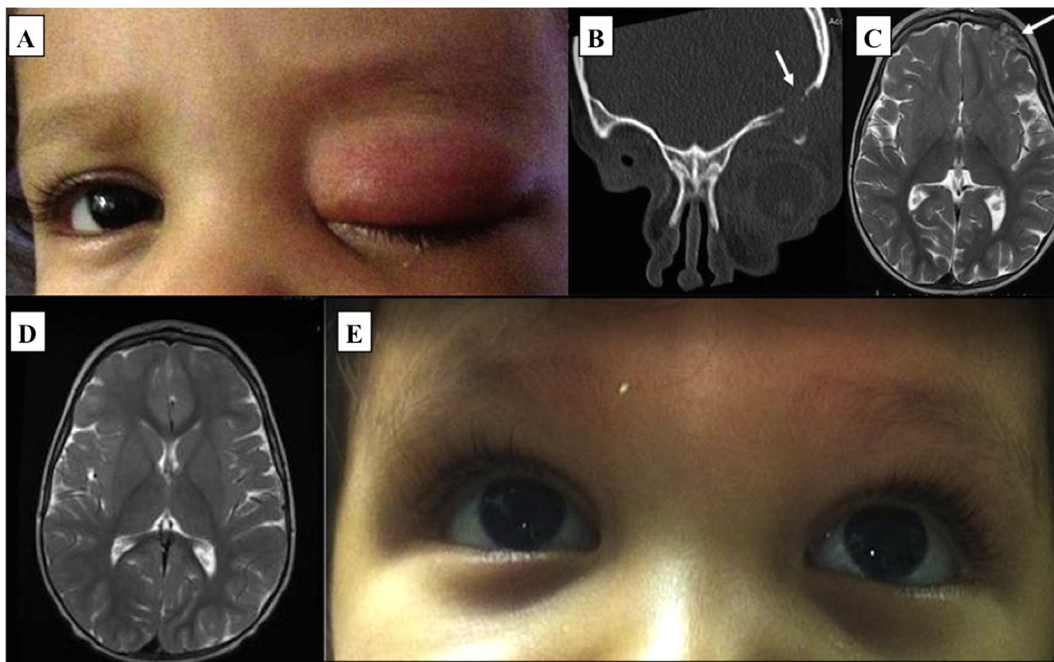


Fig. 1. (A) Lesion in the left upper eyelid demonstrates diffuse erythema and edema of the eyelid with marked proptosis. (B) Coronal CT shows a lytic lesion in the anterior, superior frontal bone of the left orbit (white arrow) with displacement of the left globe inferiorly. (C) Axial MRI shows a heterogeneous soft-tissue mass on the left anterior side with meningeal involvement (white arrow). (D) MRI performed at 7 months post-treatment of the lesion shows complete resolution of the mass after LCH-III protocol treatment. (E) Clinical photograph at 11 months shows a marked reduction in size and improvement in clinical appearance after LCH-III protocol treatment.

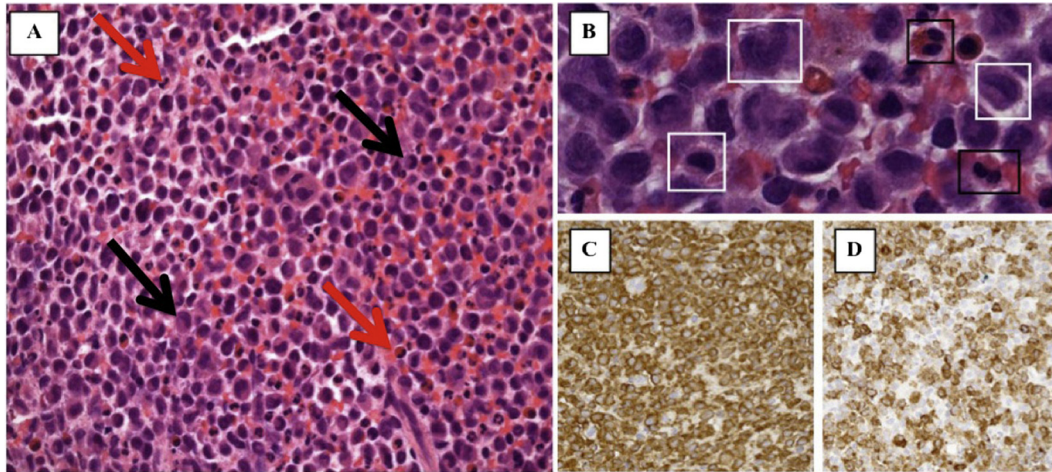


Fig. 2. (A) Dense cellular infiltrate with some large Langerhans-type cells with an indented, grooved nucleus (black arrows) in a background of eosinophils (red arrows). Hematoxylin and eosin stain. Original magnification 40 \times . (B) Langerhans-type cells (white boxes) and eosinophils (black boxes) at higher magnification. Hematoxylin and eosin stain. Original magnification 100 \times . (C) Immunohistochemical positive staining for CD1A. Original magnification 40 \times . (D) Positive staining for langerin. Original magnification 40 \times .

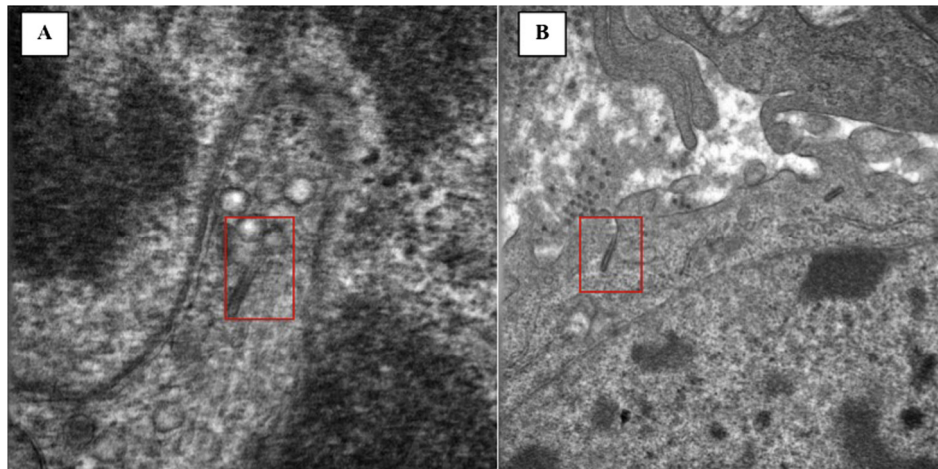


Fig. 3. (A) Electron microscopic image demonstrates Birbeck granules with a long rod inclusion and rounded, bulbed ends (red box). Original magnification 80,000 \times . (B) Electron microscopic image of invaginations of the plasma membrane with Birbeck granule formation (red box). Original magnification 30,000 \times .

Hand-Schuller-Christian disease is characterized by a triad of diabetes insipidus, exophthalmos, and lytic bone lesions.⁶ Letterer-Siwe disease is a rapidly progressive disease with a poor prognosis in which Langerhans type cells proliferate in many tissues.⁶ Eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease were initially grouped together as Histiocytosis X, which later was replaced by the term LCH. LCH is clinically divided into 2 groups: disease limited to the bone or soft tissue with a benign course and diffuse disease that progressed regardless of multiple therapeutic interventions.²

The highly variable prognosis of LCH depends on disease burden rather than histopathologic features, with unifocal disease achieving greater than 95% survival. Although lytic lesions of the bone can be typical of LCH, LCH can also involve other sites including the liver, lymph nodes, and lungs.³ Approximately half of patients present with multi-system disease.⁹

Our patient presented with a history suspicious for periorbital cellulitis secondary to an insect bite but failed to respond to intravenous antibiotics. Imaging identified a lytic bone lesion, and subsequent biopsy provided histopathological confirmation of Langerhans-type cells, altering the diagnosis from periorbital cellulitis to eosinophilic granuloma. While there may be similarities in the presentation of these two conditions, clinicians should be aware of the key distinguishing features between these diseases. First, eyelid inflammation secondary to eosinophilic granuloma typically progresses more slowly (over weeks or months) than in infectious cellulitis.^{10,11} In addition, eosinophilic granuloma is characterized by a lack of any preceding event, such as an insect bite or trauma. It does not respond to antibiotic therapy, and displays distinct imaging characteristics on CT and MRI, especially the lytic lesions of the bone.¹¹

Previous reports have described LCH associated with periorbital cellulitis in children between one to seven years old,

with our 18-month-old patient being within this age range.^{5,11,12} A young age at presentation warrants particularly careful work-up and monitoring for multi-focal involvement and malignancies, including LCH, and demands a multi-disciplinary approach that includes pediatricians specializing in hematology and oncology. Our case reinforces the need to consider imaging and alternative diagnoses in a patient with presumed periorbital cellulitis with atypical features, or in a patient who fails to respond to conventional intravenous antibiotic therapy to exclude LCH or rhabdomyosarcoma, which can clinically mimic cellulitis. This is important to consider in light of new developments suggesting that we do not yet fully understand the disease, and that LCH lesions may not actually be derived from a group of disorders involving transformation of epidermal Langerhans cells. Instead, it is possible that they represent a separate, more aggressive neoplastic process.^{4,7}

Conflict of interest

The authors declare that there is no conflict of interest.

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