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Atypical presentation of isolated orbital Langerhans cell histiocytosis

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Abstract. *Background:* A 9-year old female presented with one month of waxing and waning upper eyelid swelling. An excisional biopsy via anterior orbitotomy was performed. *Objective:* To describe a patient presenting atypically with symptoms concerning for orbital cellulitis who was diagnosed with Langerhans cell histiocytosis (LCH). *Methods:* Description of case report. *Results:* We report a case of a 9-year old female with one month of periorbital edema and erythema suspected to be orbital cellulitis. A complete ophthalmological exam, subsequent imaging, and an excisional biopsy revealed the diagnosis of LCH. With a confirmed diagnosis, the patient started chemotherapy indicated by the Histiocyte Society Evaluation and Treatment Guidelines. *Conclusion:* Langerhans cell histiocytosis (LCH) embodies a spectrum of diseases with the primary pathologic process being the abnormal proliferation of polyclonal Langerhans cells. In children with isolated bony involvement, the most common presenting symptom is pain. Rarely is orbital involvement with associated periorbital edema and erythema the primary presentation. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36 (2): 167-171)*

Key words: Langerhans cell histiocytosis, orbital tumors, pediatric tumors, bone lesions

Introduction

Langerhans cell histiocytosis (LCH) is a term used to describe a spectrum of diseases characterized by clonal proliferation of Langerhans cells which can manifest as either a unisystem or multisystem disease (1). It had previously been classified as a group of conditions under the general term "histiocytosis X". Due to improved histologic classification of LCH, it is now recognized as a disease which presents along a spectrum of severity ranging from benign isolated bone lesions to aggressive multisystem disease (2). For instance, eosinophilic granuloma presents as a solitary or multifocal lesion predominantly in older children. When characterized by lytic bone lesions of the skull, proptosis, and diabetes insipidus, it is known as Hand-Schuller-Christian disease. In children, disease characterized by multiple organ involvement associated with rash, hepatosplenomegaly, anemia, and lymphadenopathy is known as Abt-Letterer-Siwe disease and has the worst prognosis (3-5).

The typical age of onset of LCH is 1-4 years old with a median age at diagnosis of 3 years old (4), although it can be seen at any age (2, 6). The most common presenting symptom is bony pain (7). Presenting with primary symptoms arising exclusively from the orbit is uncommon (8-10). Those diagnosed when less than one year old have a worse prognosis (2). The incidence ranges from 2.6-8.9/1,000,000 children per year and 1-2/1,000,000 adults per year (1-5). It is more common in boys than girls, and

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Caucasians are the most frequently affected. Multisystem involvement and hemophagocytic syndrome are associated with a less favorable outcome (11).

The decision regarding whether LCH represents a true neoplasm versus an inflammatory disease is controversial. There is evidence that it may represent an abnormal maturation of Langerhans cells and an aberrant immune system reaction, however no specific infectious or autoimmune etiologies have been identified (1, 5). Support for LCH being a neoplastic process is provided by the co-occurrence of LCH with other malignancies such as myelodysplastic syndrome (5, 12). Histologically, LCH is characterized by clonal proliferation of Langerhans cells that resemble tissue macrophages rather than dendritic cells found in the skin (1). The infiltrate is often accompanied by eosinophils and, less frequently, lymphocytes, plasma cells, and polymorphonuclear leukocytes. Focal necrosis and fibrosis may also be present in more chronic lesions. Immunohistochemistry is used to aid in the diagnosis of LCH, with Langerhans cells being immunopositive for S100, CD1a, and CD207 (langerin) (1, 4, 5, 13). On electron microscopy, rod and tennis racket shaped bodies, called Birbeck granules, are found in the cytoplasm of Langerhans cells and are considered pathognomonic for the disease (1, 4, 12). Identification of the BRAF V600E gene mutation in LCH has become an effective tool to aid in diagnosis (1, 4, 14). Bone is the most frequently involved tissue, but skin, lymph nodes, spleen, lung, liver, brain and gastrointestinal tract involvement is also seen (2). Of all bony lesions, the most common site is the skull, followed by the femur, mandible, and pelvis (4). Here, we present a case report of LCH involving the orbit in a pediatric patient.

Case Report

All patient health information was collected and evaluated in a HIPAA-compliant manner, and this research adhered to the tenets of the Declaration of Helsinki.

A nine year old African-American female was transferred to the Virginia Commonwealth University (VCU) Medical Center for further management of presumed orbital cellulitis. The patient and mother reported a one month history of waxing and waning left upper eyelid swelling that did not resolve with warm compresses or a 10 day course of oral cefdinir prescribed for preseptal cellulitis. The patient denied any pain or tenderness. The patient's history was significant for allergic rhinitis and a recent dental surgery with placement of a palate expander. Despite treatment with a bactericidal antibiotic, her upper eyelid edema did not resolve. She was therefore brought to an outside hospital emergency room where computed tomography (CT) of the head was obtained and showed findings concerning for frontal sinusitis with extension of inflammation into the left superior orbit. CT imaging was repeated upon transfer to VCU and is presented in Figure 1.

At presentation, the patient was afebrile. Upon examination, her Snellen visual acuity without correction at near was 20/20. Ishihara color plates were full in both eyes. No relative afferent pupillary defect was appreciated, and intraocular pressures obtained with tonopen were 15 mmHg on the right and 16 mmHg on the left. She had minimal periorbital swelling of the left upper eyelid with no erythema or tenderness to palpation. Hertel exophthalmometry measurements were equal at 16 mm bilaterally at a base of 92 mm indicating no proptosis. Her CRP was 0.5 mg/dl (reference range 0-0.5 mg/dl) and ESR was 3 mm in 1 hr (reference range 0-10 mm). No leukocytosis was present. Blood cultures were negative for bacteria or fungi.

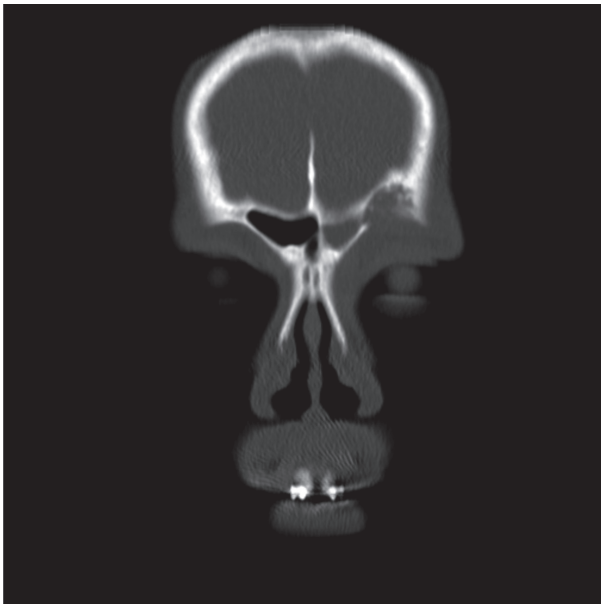


Fig. 1. Coronal view of CT of the head showing left frontal sinusitis with superior orbital extension and bony erosion

The repeat CT scan obtained upon admission with the addition of contrast suggested a soft tissue lesion of the left superior orbit and redemonstrated the osseous remodeling and destruction demonstrated on outside imaging. Magnetic resonance imaging (MRI) of the head and orbit, both with and without gadolinium, was then obtained to better characterize the lesion. MRI showed a 9 x 17 x 12 mm left superior orbital lesion with adjacent thickening and enhancement of the dura but no further extension into the brain parenchyma (Figures 2, 3). The decision was made to perform an excisional biopsy via an anterior orbitotomy without bone flap. Intraoperatively, a bony defect measuring approximately 17 mm in an anterior-posterior direction and 15 mm horizontally was explored with excision of a friable lesion with initial frozen sections revealing chronic inflammatory cells. The lesion directly communicated with both the frontal sinus and frontal lobe dura and was bluntly dissected free, keeping the dural plane intact. The edges of the bony defect were malleable and thinned.

The diagnosis of LCH was confirmed by pathology, discussed further in the next section. It was confirmed the patient only had involvement of the aforementioned sites with a negative chest radiograph, complete skeletal survey, and laboratory evaluation. Despite the fact that lytic bone lesions only become apparent when at least a third of the density is lost, radiography remains the gold standard of the diagnostic and staging procedure. The patient followed up with pediatric hematology-oncology who started her on vinblastine and prednisone according to the LCH III protocol. Since initiation of treatment, the patient's orbital symptoms of eyelid swelling and erythema have completely resolved. She has maintained 20/20 best corrected Snellen visual acuity and full Ishihara color plates. Repeat MRI eight months after starting treatment displayed no recurrence of the mass and the patient has not had a BRAF gene mutation investigation.

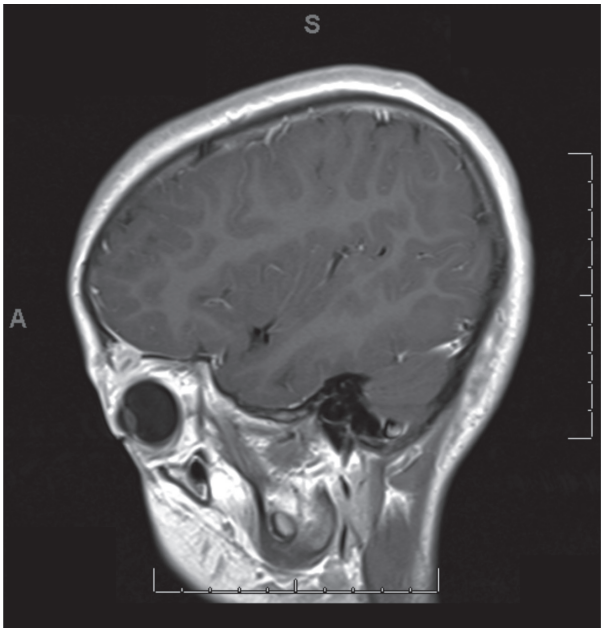


Fig. 2. Transverse cut of brain MRI showing left superior orbital mass with adjacent dural enhancement

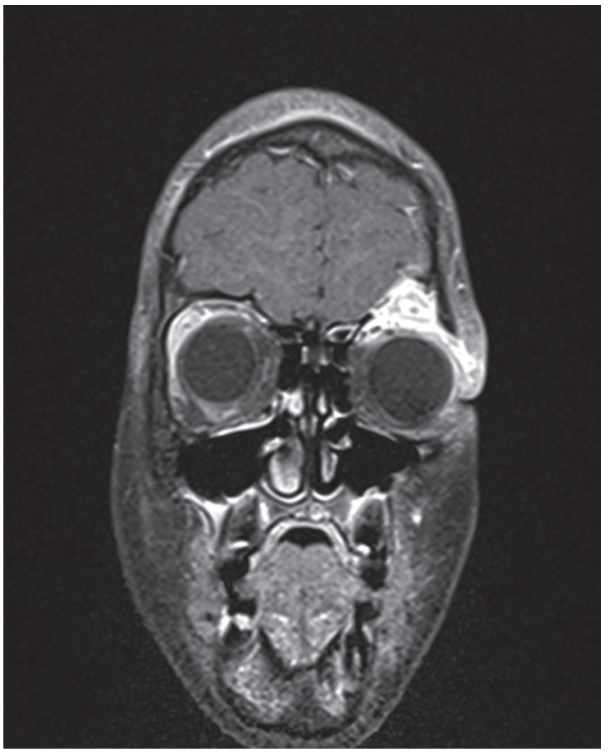


Fig. 3. Coronal cut of Brain MRI showing superior orbital lesion

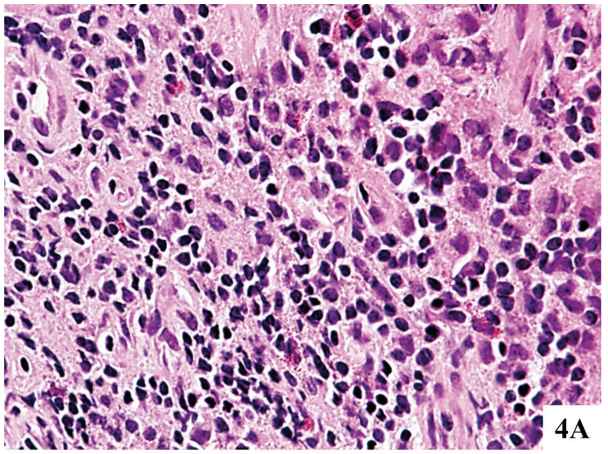
Histopathology

Microscopically there are sheets of neoplastic cells with scattered eosinophils, plasma cells and multinucleated giant cells. The neoplastic cells have elongated or clefted nuclei with occasional nuclear grooves and inconspicuous nuclei (Figures 4A-4B). Mitotic activity is low (1-2 mitoses/10HPF). No necrosis is present. The neoplastic cells are strongly pos-

itive for CD1a (Fig. 4C) and focally positive for s100 (Fig. 4D). These features are most consistent with a diagnosis of Langerhans cell histiocytosis. Several other entities that may have overlapping morphological appearance should be considered in the differential diagnoses, which include Rosai-Dorfman disease, Erdheim Chester disease, and non-specific chronic inflammation (inflammatory pseudotumor). Rosai-Dorfman disease shows large and pale histiocytes with empripolesis (engulfment of lymphocytes) and the histiocytes are usually s100 positive and CD1a negative. There are no Langerhans cells in Erdheim Chester disease and the histiocytes in this entity are negative for both CD1a and s100. For non-specific chronic inflammation (inflammatory pseudotumor), there is usually a mixed population of inflammatory cells without CD1a positive Langerhans cells.

Discussion

The reported incidence of orbital involvement in all forms of LCH is variable but has been reported to be as high as 37.5% and is usually seen in patients with chronic lesions (2, 4, 5). The most common ocular adnexal manifestation of LCH is an isolated orbital infiltrate and is typically unilateral (1). Involved structures may include the eyelid, conjunctiva, caruncle, choroid, and the optic nerve. Orbital apex syndrome, cavernous sinus syndrome, and sarcoidosis



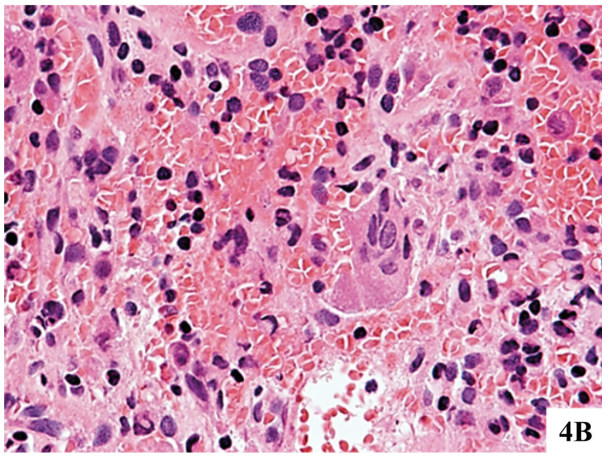
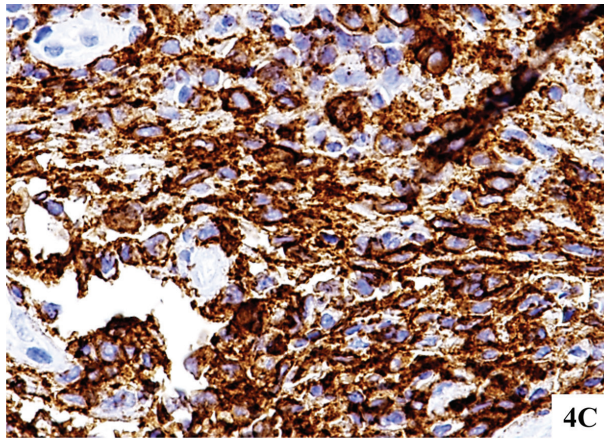


Fig. 4A-4B. H&E sections of the orbital lesion. Magnification 4A: 10X; 4B: 20X. H&E sections show sheets of neoplastic cells with scattered eosinophils, plasma cells and multinucleated giant cells. The neoplastic cells have elongated or clefted nuclei with occasional nuclear grooves and inconspicuous nuclei



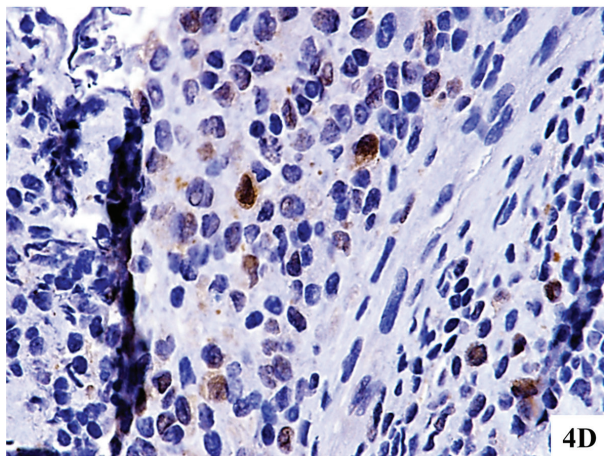


Fig. 4C-4D Immunohistochemical staining. 4C: CD1a; 4D: s100. Magnification at 20X. The neoplastic cells are strongly positive for CD1a and focally positive for s100

are also possible (15, 16). Orbital LCH typically presents as an isolated bone lesion and soft tissue mass, most typically superiorly or superotemporally along the orbital roof. This may lead to proptosis as well as periorbital erythema and edema, mimicking an infectious process. Additional symptoms may include blurred vision, diplopia, and potentially the development of amblyopia in children. Orbital imaging classically shows "punched out" lytic lesions of the bone with an associated soft tissue lesion (17).

The differential for orbital LCH includes periorbital or orbital cellulitis, a ruptured dermoid cyst, sarcoidosis, idiopathic orbital inflammatory syndrome, and other malignant processes such as leukemia, neuroblastoma, and rhabdomyosarcoma (1). The absence of any history of pulmonary sequelae, ophthalmoplegia, diplopia, ptosis, pupillary changes, and other neurological manifestations makes sarcoidosis and neurosarcoidosis less likely (16). The diagnosis of LCH is established by incisional or excisional biopsy. Due to the rarity of the condition, treatment often varies on an individual case basis, however there are treatment algorithms available (18). For isolated caruncular and eyelid lesions, excision may successfully treat the disease. Excision in combination with intralesional steroids for isolated orbital lesions have also been used effectively, as high doses of steroids are thought to inhibit osteolysis (19). Chemotherapy can be used for multifocal disease or for orbital lesions with dural involvement, with the most common agents being vinblastine, prednisone, etoposide, and methotrexate. Radiation can be used to treat disease recurrence. Lastly, bone marrow transplant and immunoglobulin therapy have been used for uncontrolled disease recurrences and CNS involvement (1). After treatment, disease recurrence is most common within 12-18 months, although there are case reports of recurrence over 10 years later (20). The prognosis for patients with limited orbital involvement is favorable (1, 2).

LCH is an important consideration for patients presenting with a chronic orbital process. Here, we have discussed a pediatric patient with an initial presentation concerning for an infectious process, however the chronicity and lack of response to initial, bactericidal antibiotic therapy raised the suspicion for a non-infectious process. As discussed earlier, the most common presenting symptom in children with isolated bony involvement is pain, however this case was unique in that the patient denied any pain or tenderness. This case demonstrates the importance of maintaining a high index of suspicion for alternate diagnoses when evaluating patients for presumed orbital infections.

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