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Case Report

Orbital Edema Secondary to a Sphenoidal Mass as the Presenting Symptom of High-Risk Precursor B-Cell Acute Lymphoblastic Leukemia

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Leukemia · Orbital edema · Orbital mass

Abstract
Introduction: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, known to present with ocular manifestations in rare cases. ***Case Presentation:*** We describe the case of a 9-year-old previously healthy male who developed a 2-day history of periocular swelling and was found on MRI to have a large sphenoidal mass. Further work up showed involvement of the spinal cord, iliac crests, and kidneys. His initial blood work showed no hematological abnormalities. A bone marrow biopsy taken from the iliac crest demonstrated >90% B lymphoblasts and flow cytometry was positive for CD19. Overall, his investigations were consistent with a diagnosis of precursor B-cell ALL (pre B-ALL). His neuro-ophthalmic exam showed right-sided subtle periocular edema, decreased palpebral fissure height, and proptosis. Posterior exam showed mild nasal elevation of the right optic disc without vessel obscuration and mild tortuosity of the peripheral vessels. He otherwise had no overt signs of afferent or efferent dysfunction despite the proximity of the mass to his optic nerve and globe. ***Conclusion:*** This case demonstrates that high-risk pre B-ALL, a childhood cancer not commonly associated with orbital manifestations, can present with orbital edema and normal leukocyte count in an otherwise healthy child.

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy comprising 30% of all childhood malignancies [1]. Its clinical presentation can be nonspecific but more than half of children exhibit at least one of the following features: hepatomegaly, lymphadenopathy, fever, musculoskeletal pain, or hematological abnormalities and their physical manifestations such as bruising [1]. Ocular manifestations of leukemia have been well described, involving infiltration or hemorrhage of the retina, optic nerve, or orbit [2]. However, these are typically in the setting of known leukemia; it is rare for ocular manifestations to be the initial sole presenting complaint. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534926).

Case Description

A 9-year-old previously healthy male developed a 2-day history of right eye periocular swelling, foreign body sensation, and watery discharge. He also endorsed intermittent diplopia, which was resolved on presentation, and was unsure if it was binocular or monocular. He had an unremarkable birth and family history. Review of systems revealed a spontaneously resolved fever prior to presentation, measured via a single axillary temperature of 39°C. He was initially seen at a rural community hospital where he received a single dose of IV antibiotics for concern of preseptal cellulitis. He continued to worsen despite IV antibiotics which prompted a CT scan that showed an extracranial sphenoid wing mass with erosion of the temporal and sphenoid bone. Given the orbital location and appearance of the mass was suspicious for a noninfectious etiology, the patient was then transported to a pediatric tertiary care hospital for neurosurgical and ophthalmology assessment.

His initial ophthalmic exam was notable for visual acuity of 20/20 in both eyes. Pertinent positive findings included right-sided mild periocular edema, right eyelid tenderness, decreased right palpebral fissure height, and proptosis (Fig. 1). Hertel exophthalmometer measurements were 19 mm OD and 13 mm OS with a base of 97 mm. His posterior segment showed mild nasal elevation of the right optic disc without vessel obscuration and mild tortuosity of the peripheral vessels (Fig. 2). Pertinent negative findings included no relative afferent pupillary defect, normal intraocular pressure, no color vision deficit, full extraocular movements, no strabismus, normal anterior segment, and normal 30-2 Humphrey visual field in the right eye.

His investigations showed a normal leukocyte count ($8.1*10^9$ cells/L, reference range 4.2–11.5 $*10^9$ cells/L), hemoglobin (115 g/L, reference range 105–135 g/L), potassium (4.0 mmol/L, reference range 3.5–5.1 mmol/L), and uric acid (160 μmol/L, reference range 96–296 μmol/L). His C-reactive protein was elevated (91.8 mg/L, reference range <10.0 mg/L). There was concern for a malignant etiology given the bony erosion on imaging, rapid onset, elevated C-reactive protein in the absence of leukocytosis. The patient then underwent an MRI of the head and spine with contrast which showed a right-sided soft tissue mass (5.4 × 6.8 × 7.0 cm) centered on the sphenoid bone with extension into the right orbit (Fig. 3a). The right lateral rectus muscle and optic nerve were displaced with radiographic evidence of proptosis. The mass showed low-intermediate signal on T1, mild hyperintensity on T2 with some foci of higher signal, and restricted diffusion throughout the lesion. Given the wide differential diagnosis at this point, systemic imaging was obtained to look for any additional lesions. MRI of the spine showed multiple bilateral solid kidney lesions and diffused hyperintense T2 signal and enhancement in the vertebral bodies of L1 and S1, left sacroiliac joint, and right iliac crest.

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Fig. 1. Clinical presentation. External photograph showing subtle right-sided periocular edema. Hertel exophthalmometer measurements were 19 mm OD and 13 mm OS with a base of 97 mm.

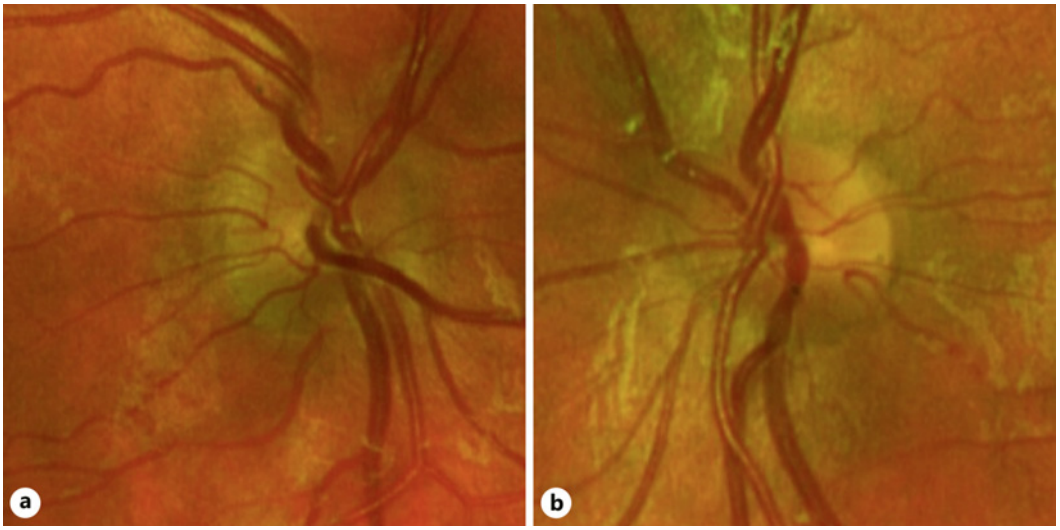

Fig. 2. Pseudocolor images of the right (**a**) and left (**b**) eye. There is slight nasal elevation of the right compared to left optic disc margin.

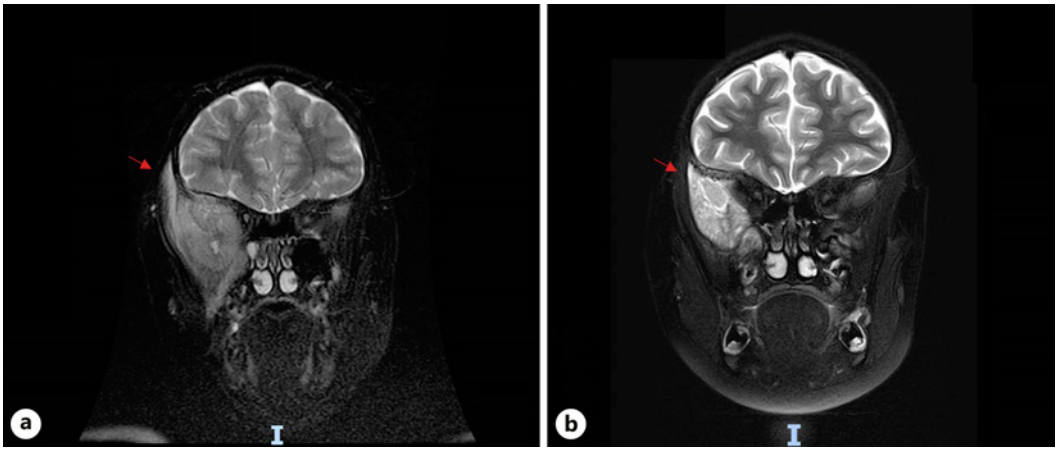

Fig. 3. MRI of head and spine before and after chemotherapy induction with Children's Oncology Group protocol AALL1732 for high-risk pre B-ALL. Red arrows indicate mass. **a** Initial T2 sequence coronal view showing large soft tissue mass centered in the right infratemporal fossa with intracranial, extracranial, subtemporal, and extraconal extension. Right optic nerve and right lateral rectus muscle displacement medially with proptosis. **b** Red arrows indicate mass. T2 sequence coronal view of soft tissue mass with interval improvement of soft tissue mass centered in the right infratemporal fossa with intracranial, extracranial, subtemporal, and extraconal extension.

A bone marrow aspirate was taken from the iliac crest which showed >90% B lymphoblasts. A lumbar puncture was negative for blast cells, flow cytometry was positive for CD19 and variable for CD10 and CD20, and cytogenetics showed the dup(1q) abnormality. Overall, his investigations were consistent with a diagnosis of precursor B cell ALL (pre B-ALL). He was considered high risk given ocular and intracranial involvement. The patient was enrolled and treated on Children's Oncology Group (COG) protocol AALL1732, a Phase 3 randomized trial of Inotuzumab Ozogamicin for newly diagnosed high-risk B-ALL [3]. In short, this trial aims to determine if addition of two blocks of inotuzumab ozogamicin to COG-modified Berlin-Frankfurt-Munster (BFM) chemotherapy, a standardized efficacious regimen, will improve outcomes in children and young adults with B-ALL [4]. Repeat MRI head following induction showed a marked interval decrease in size of the sphenoidal mass and complete resolution of the intracranial and intra-axial extension (Fig. 3b). There was decreased mass effect of the right lateral rectus muscle but persistent mild radiographic proptosis. Eleven months after presentation, while still on chemotherapy, he has had no significant adverse events and on MRI the sphenoid mass continued to improve measuring 3.9 × 1.7 × 1.7 cm from 5.4 × 6.8 × 7.0 cm on presentation.

Conclusion

This case demonstrates that high-risk pre B-ALL can present with orbital edema as the main complaint and a normal leukocyte count in an otherwise healthy child. This patient lacked all the most common presenting symptoms of B-ALL including B symptoms, easy bruising, fatigue, dyspnea, infection, or enlargement of extramedullary sites. He is also older than the peak incidence of 2–5 years. The patient lacked laboratory evidence of a hematologic process, such as abnormal peripheral blood cell counts, which can delay the diagnosis of leukemia. In this case, the diagnosis was made through bone marrow biopsy which happened to be the first biopsy site. The team preferred not to biopsy the orbital lesion if it could be avoided so the potential extraocular biopsy sites were the kidney, vertebral bodies of L1 and S1, left sacroiliac joint, and right iliac crest. The plan was to first biopsy the bone marrow as it is logistically easier to organize at the treating institution and if the bone marrow biopsy was negative, then the kidney would have been biopsied. Imaging findings of disease involving the cranium, spinal column, and kidney were suggestive of a malignant process with a broad differential including both hematologic and solid malignancies. Given the rapid onset and orbital location, other solid tumors such as a rhabdomyosarcoma, the most common primary orbital neoplasm in children, would be important to rule out despite renal involvement being less likely in this condition. While cranial nerve deficits are common with CNS involvement in ALL, fortunately, this patient's afferent and efferent visual function was unaffected. The subtle disc elevation might foreshadow impending optic nerve compromise when taken into context the extent of orbital involvement on MRI.

Leukemia can have a variety of ocular manifestations that ophthalmologists should be aware of that can relate to primary infiltration of ocular or adnexal structures by tumor cells, secondary system manifestations of the disease, or adverse effects due to treatment. Likelihood of ocular involvement also depends on the type of leukemia which can be broadly classified by the affected cell type – namely leukocytes causing ALL and myelocytes causing acute myeloid leukemia. A study of 288 leukemia patients found that ocular changes were more common in myeloid leukemias (41%) compared to lymphoid leukemia (29.2%) [5]. Masses outside the bone marrow in acute myeloid leukemia, otherwise called chloromas, affecting the orbit are also more common (77.8% of patients) compared to ALL (18.5%) [6]. These findings add to the novelty of the presented case of an orbital mass in ALL. Secondary ocular complications of leukemia include "leukemic retinopathy," the most common ocular

manifestation of leukemia, which is related to hematologic abnormalities causing reduced retinal blood flow and vascular stagnation [7]. This can result in retinal capillary dropout and microaneurysm formation. Other secondary ocular effects include papilledema due to infiltration of the CNS or optic nerve by tumor cells [7]. High-dose steroids are often involved in leukemia treatment which can cause ocular hypertension and cataract [8].

This case differs from existing reports of B-ALL presenting as orbital edema in the lack of laboratory abnormalities and other symptoms, reporting of a full neuro-ophthalmic assessment, as well as imaging demonstrating the interval resolution of the orbital mass with treatment. Previously published case reports describe this rare manifestation of B-ALL with a subacute periocular edema or proptosis in the setting of concurrent B symptoms and marked hematological abnormalities [9, 10]. Alford et al. [11] describe a case of a 12-year-old male with orbital involvement in pre B-ALL that presented as an intraconal mass. The diagnosis in this case was established via biopsy of the orbital mass – which depending on the location can present significant risks compared to other means of diagnosing leukemia such as a bone marrow biopsy as done in our case [11]. Sathitsamitphong et al. [9] presented a case of a 3-year-old girl diagnosed with pre B-ALL in setting of 10 days of progressive painless right eye proptosis. The child was otherwise asymptomatic but had classic hematological abnormalities of a leukemia including an elevated leukocyte count of $42*10^9$ cells/L and low hemoglobin. Stein et al. [12] reported a similar case of a 9-year-old girl presenting with periocular edema as the sole presenting symptom of B-ALL. However, the report lacked the patient's ophthalmic exam to confirm whether there were other ocular findings and response to treatment. There have been more severe cases of B-ALL with orbital involvement reported including an 11-year-old female with a large soft tissue mass affecting both orbits resulting in bilateral optic disc edema, orbital swelling, and retinal flame hemorrhages [13]. Similar to previous cases, this patient was considered to have intracranial involvement given the proximity of the mass to the orbit [14]. The absence of blasts in the cerebrospinal fluid is a finding that has also been shown in other cases of ALL presenting with an orbital mass [15]. A limitation of this case is the relatively short follow up interval but thus far the patient has shown good response to treatment. This is in keeping with the outcomes of pediatric ALL being generally good with over 80% of patients being cured with multiagent regimens [16]. Even amongst high-risk cases, the estimated 4-year event-free survival is approximately 76% [17].

In conclusion, this case illustrates the need for a broad differential diagnosis for periocular edema in a child. In cases without infectious features or nonresponsive to antibiotics, primary or metastatic malignancies must be considered. Early neuroimaging enabled this patient to be referred to appropriate specialty services. Systemic imaging, despite being asymptomatic with normal laboratory investigations, proved to be valuable in avoiding neurosurgical or orbital intervention in this case. It is critical for ophthalmologists to recognize the atypical ocular presentations of childhood malignancies.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the father of the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors (C.L., R.A., J.T.D., Z.X.F., and A.V.F.) contributed intellectually to the content and writing of this case report.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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