VISUAL DIAGNOSIS

What's in an Eye?

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PRESENTATION

An 18-month-old healthy boy is brought to the emergency department (ED) with a 3-day history of swelling, redness, and discharge from the left eye (Fig 1). His pediatrician had diagnosed conjunctivitis on first day of illness and started treatment with polymyxin B/trimethoprim eye drops. Over the next 2 days, the swelling worsened over the left eyelid, despite using the drops. On day 3, he has decreased oral intake and increased fussiness. His parents think he may have also fallen at daycare sometime during these 2 days. They report no loss of consciousness, vomiting, or change in mental status due to the suspected fall. The child does not complain about pain. He has no fever, no runny nose, and no cough. The right eye remains unaffected. With concern for worsening eyelid swelling, he is brought to the ED.

The patient was born at full term to a primigravida healthy mother. There were no pregnancy or delivery complications, and no risk factors related to prenatal laboratory results. The patient has no significant past medical history, takes no medications apart from eye drops, has no prior hospitalizations, and immunizations are up to date. An assessment of the child's social history reveals that the parents are divorced and the patient lives with grandmother and mother; however, both parents are present in the ED.

On arrival at the ED, the patient's vital signs are normal for age (rectal temperature, 99.7°F [37.6°C]; heart rate, 120 beats/min; respiratory rate, 30 breaths/min; blood pressure, 90/70 mm Hg; oxygen saturation, 98% on room air). With examination, he appears uncomfortable, tired, and fussy but is consolable by his mother. He is lying in her arms with significant left eyelid swelling and redness (Fig 2). The left eye conjunctiva, pupil, and retina are not visualized due to soft tissue swelling, but proptosis is suspected. Upper and lower eyelids are warm and tender to palpation. No bruising is noticed around the eye. Further examination is limited due to the lack of patient cooperation. The right eye is found to have spontaneous opening, normal conjunctiva, normal tracking, pupil reactive to light, and full extraocular movement present; however, the right red reflex is absent. The rest of the examination is normal.

Laboratory evaluation includes a complete blood cell count, comprehensive metabolic panel, and blood culture. There is leukocytosis of 15.9 (neutrophils 57%, lymphocyte 29%, and monocytes 10.8%). Other laboratory tests are normal. Computed tomography (CT) scan of the orbit is obtained to evaluate for orbital cellulitis and reveals possible open globe rupture with intraocular calcifications (Fig 3). The history of possible trauma without medical intervention and

AUTHOR DISCLOSURE Drs Gupta and Menoch have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

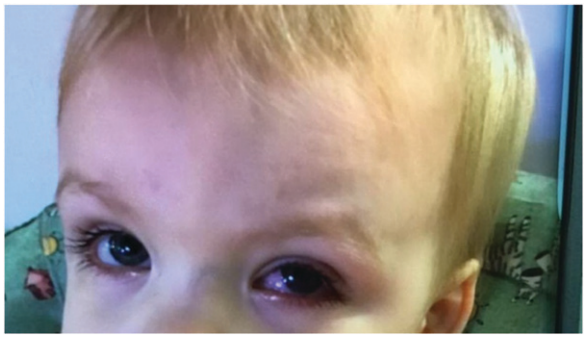

Figure 1. Day 1 of illness. There is mild redness of left eye.

imaging suggestive of globe rupture leads to notification of Child Protective Services and transfer to a tertiary care hospital for further management by ophthalmology.

The patient has an ophthalmology evaluation under sedation. External examination of the right eye reveals normal tracking, full extraocular range of movement, pupils reacting from 5 mm to 3 mm, and intraocular pressure of 16 mm Hg. The anterior segment has normal conjunctiva, cornea, sclera, iris, anterior chamber, and lens. With dilation, the posterior chamber of right eye is found to have clear media, a sharp optic disc, a flat macula with no cherry red spot, tortuosity of vessels, and a large protuberant white mass on the nasal side of the optic disc with feeder vessels but no retinal hemorrhages. External examination of the left eye is limited due to extensive periorbital edema; intraocular pressure is 47 mm Hg (normal, 12–22 mm Hg). The anterior segment has 360-degree bullous chemosis and stromal haze with visible proptosis. Lens and iris assessments are not possible due to the stromal haze and periorbital swelling. The ophthalmologist is also unable to examine the posterior chamber of left eye due to the swelling.

Review of the CT scan by a neuroradiologist reveals the diagnosis.

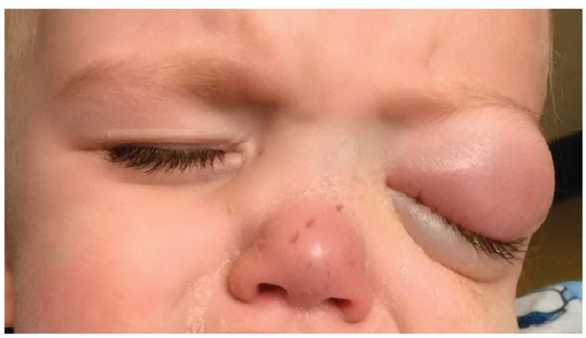

Figure 2. Day 3 of illness. There is extensive left-sided periorbital edema in an irritable child.

DIAGNOSIS

The differential diagnosis for acute eyelid swelling in childhood can generally be categorized as infectious and noninfectious. Infectious causes include conjunctivitis, preseptal cellulitis, and orbital cellulitis. The noninfectious causes can be traumatic (mechanical trauma from eye rubbing, basilar skull fracture, contusion or orbital wall/facial bone fracture, globe rupture), conjunctivitis, sty, inset bite, allergic reaction, dacryocystitis, edema due to nephrotic or nephritic syndrome, and neoplastic (neuroblastoma, rhabdomyosarcoma, retinoblastoma [RB]) diseases. Conjunctivitis, allergic reaction, nephrotic syndrome, and neoplastic diseases may present with bilateral eyelid swelling.

Based on the patient's history and physical examination the differential diagnosis was narrowed to traumatic injury with superimposed infection. When the globe cannot be visualized due to extreme soft tissue swelling, or if the patient appears toxic, imaging is required to diagnose and evaluate the problem further. For this patient, the diagnosis was concerning for both infection due to warmth and redness, along with trauma due to the initial CT scan read and vague history of a fall.

Bilateral interocular calcifications suggest a diagnosis of bilateral RB with left-sided orbital cellulitis (Fig 4).

DISCUSSION

RB is the most common intraocular malignancy of childhood, with an incidence of 1 in every 15,000 children. (1) The median age of diagnosis is between 18 and 20 months with an average age of 12 months for children with bilateral disease and 24 months for children with unilateral disease. (2) One-third of RB cases are bilateral. (3) RB occurs in both heritable and nonheritable forms. Heritable forms result from germline mutations in the *RB1* gene, which is associated with all bilateral RB and 15% of unilateral RB. Nonheritable RB is caused by new somatic mutations in 1 retinal cell, from which the tumor arises. Less than 10% of patients with RB have a positive family history for the disease, suggesting that most cases arise from somatic mutations. If a germline genetic mutation is identified in a family member, children should have routine screening to facilitate early detection and treatment of disease. (4) Patients with RB typically present with leukocoria (60% of cases), (5) but may present as strabismus or visual impairment. (6) Orbital cellulitis is an infrequent (4%–5%) presentation of RB. (7)(8)(9)

The American Academy of Pediatrics recommends a red reflex screening test with each examination for all children from birth through 2 years of age. (10) However,

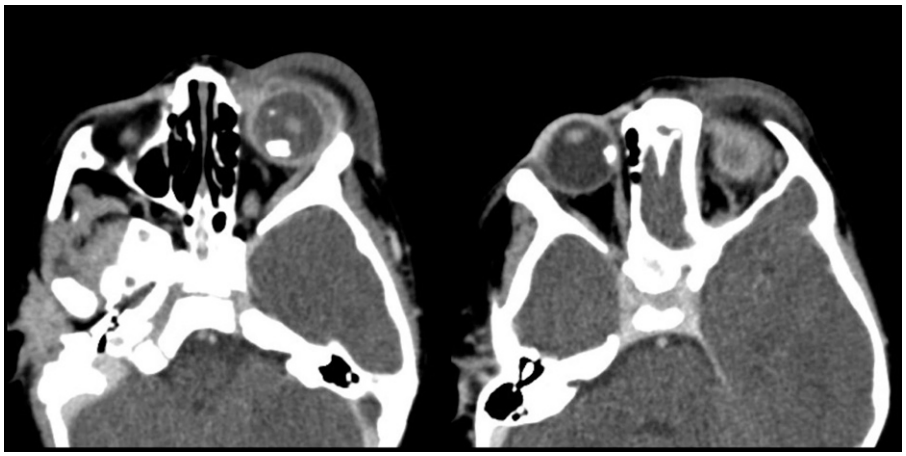

Figure 3. Axial computed tomography scan of the orbits with contrast.

unilateral RB may present as late as 5 years of age, and rare cases have been reported at 18 years of age and in adults. (11)(12)(13) An absent or asymmetric red reflex examination in any eye should prompt the evaluation for RB by an ophthalmologist. (10)

In January 2018, the American Academy of Pediatrics endorsed screening recommendations for children from birth to age 7 who are at risk for RB. (14) "At risk" was defined as having a parent, sibling, or first- or second-degree relative with the disease. Genetic testing is important in children with a family history to determine their risk for RB. If an *RB1* mutation is found, the risk is near 100%. "A consensus statement from the American Academy of Ophthalmic Oncologists and Pathologists recommends:

- Dedicated ophthalmic screening is recommended for all children at risk for retinoblastoma above the population risk.
- Frequency of examinations is adjusted on the basis of expected risk for *RB1* mutation.
- Genetic counseling and testing clarify the risk for retinoblastoma in children with a family history of the disease.
- Examination schedules are stratified on the basis of high-, intermediate-, and low-risk children.
- Children at high risk for retinoblastoma require more frequent screening, which may preferentially be examinations under anesthesia." (14)

The evaluation should consist of a complete physical examination, ophthalmologic examination under anesthesia, ocular ultrasonography, and magnetic resonance imaging of the brain and orbits. A CT scan is not recommended for diagnosis because of the risk of radiation-induced second cancers in patients with heritable disease. (15) Intraocular calcifications can be seen with ultrasonography, and this is sufficient for referral to an ophthalmologist for dilated eye examination under sedation, which is the preferred method (ie, direct visualization) of diagnosis. (6)(16) Magnetic resonance imaging of brain should be obtained for all patients

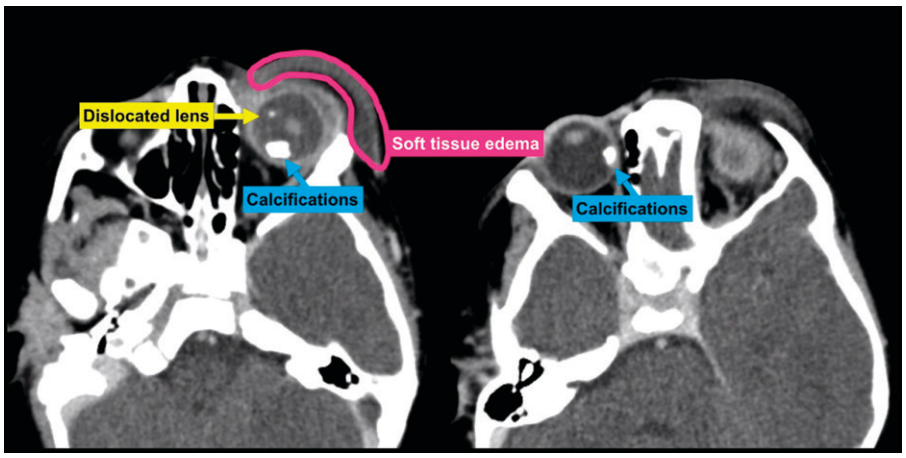

Figure 4. Axial computed tomography scan orbits with contrast marked to show swelling (soft tissue edema) around the left eye and a dense calcification and dislocated lens within the left globe. The right eye contains a dense calcification within the globe without lens dislocation.

with RB to rule out associated intracranial tumors, most commonly, pineoblastoma, also known as trilateral RB. (17)

Often the diagnosis is confused with nonaccidental trauma, especially if there are CT findings of possible globe rupture with uncertain trauma history. This was the case with our patient. An absent red reflex in the contralateral eye should raise the suspicion for bilateral RB (bilateral red reflex absent in our patient). A calcified intraocular mass seen on CT scan can be due to RB, cataract, asteroid hyalosis, meningioma, retrolental fibroplasia, coats disease, cytomegalovirus retinitis, and toxoplasma chorioretinitis can rarely develop calcifications as late sequelae beyond 3 years of age. However, in a young child, calcifications in the eye is diagnostic of RB until proven otherwise. (18)

Preseptal or orbital cellulitis from tumor necrosis are rare presenting features of intraocular RB. (3)(8)(9) Some conditions may coexist and mask RB, such as conjunctivitis, steamy corneas, uveitis, and rubeosis iridis. (8)(19)(20) In these cases, a CT scan may provide vital information of extraocular extension of the tumor. (8)

Elevated intraocular pressure may be caused by tumor cells or tumor necrotic products blocking trabecular channels in the anterior chamber. This can lead to a presentation similar to globe compromise. (21)(22) Care is needed to prevent globe rupture when examining the eye under sedation.

Treatment with intravenous steroids and broad-spectrum antibiotics diminishes the orbital swelling markedly and facilitates subsequent enucleation. (7)

PATIENT COURSE

The patient was admitted to the hospital. He received broad-spectrum antibiotics for orbital cellulitis for 7 days and ophthalmic drops—dorzolamide/timolol and latanoprost—to decrease intraocular pressure. The patient had considerable improvement in left orbital erythema/edema by hospital day 3. He then underwent enucleation of the left globe and chemotherapy for RB.

Summary

- Evaluation of eye swelling requires a broad differential and a detailed yet cautious eye examination.
- Red reflex screening should be performed in all children younger than 2 years of age. (10)
- Calcifications within the eye suggests RB even in the presence of other ocular pathology. (6)(7)(8)(9)

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