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Anterior chamber fluorescein leakage in a child with intraocular pressure elevation and vitreous hemorrhage

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ABSTRACT

Purpose: To report a case of a child with neovascular and ghost cell glaucoma in the setting of previously treated vitreous hemorrhage with unique fluorescein leakage from abnormal iris vessels ultimately preventing successful fluorescein angiography.

Observations: A 3-year-9-month-old female with a medical history of very high-risk B-cell acute lymphoblastic leukemia presented with eye pain and was noted to have a complete vitreous hemorrhage and intraocular pressure elevation in the right eye which was refractory to maximum medical therapy and vitrectomy. Following vitreous hemorrhage resolution, an examination under anesthesia with fluorescein angiography was found to have diffuse leakage of fluorescein into the anterior chamber, presumably due to the active iris neovascularization. This anterior chamber fluorescein signal prevented visualization of the retinal vasculature. The patient was diagnosed with mixed mechanism glaucoma (neovascular and ghost cell) due to a resolved vitreous hemorrhage in the setting of a presumed prior ischemic event.

Conclusions and Importance: We report a case of an unsuccessful fluorescein angiogram in the setting of anterior chamber fluorescein leakage due to active iris neovascularization, and review considerations for the differential diagnosis and useful diagnostic tests in this clinical scenario.

1. Introduction

Vitreous hemorrhage, although well described in adults, is rare in children.[1] The common causes of vitreous hemorrhage in adults, such as posterior vitreous detachment, diabetic retinopathy, and retinal vein occlusion,[2] are uncommon in children.[3] The most common causes of vitreous hemorrhage in children include trauma, non-accidental trauma, and spontaneous etiologies.[4,5] Children with leukemia, on the other hand, commonly present with intraocular involvement such as cotton-wool spots, Roth spots, vascular occlusions, as well as preretinal and intraretinal hemorrhages.[6,7] These manifestations can be the result of the disease process or the chemotherapeutic agents used to treat it. The diagnosis and management of vitreous hemorrhages in children can be difficult due to the child's inability to note or describe their visual symptoms as well as poor cooperation limiting examination and diagnostics findings.[1] Vitreous hemorrhage can also present with elevated intraocular pressure (IOP) due to a variety of mechanisms including neovascular glaucoma, hemolytic glaucoma, and ghost cell glaucoma.[8] Fluorescein angiography, a procedure which allows direct visualization of the retinal vasculature, is often diagnostic in these situations, though can require general anesthesia in children in order to obtain high-quality images.[9]

We report a case of a child with leukemia who was diagnosed with neovascular and ghost cell glaucoma following a vitreous hemorrhage in the setting of a presumed retinal ischemic event. We present fluorescein angiography images and describe a unique scenario in which the retinal vasculature was not visualized due to an extensive amount of fluorescein leaking from abnormal iris neovascularization.

2. Case report

A 3-year-9-month-old female with a medical history of very high-risk B-cell acute lymphoblastic leukemia (ALL) was referred to our clinic for evaluation and management of unilateral vitreous hemorrhage and intraocular pressure (IOP) elevation. The patient was born full-term and had no additional medical history.

She was initially diagnosed with ALL 4 months prior to presentation, after a 2-week period of experiencing progressive fatigue, weight loss,

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pallor, bruising, abdominal pain, and fever. Bone marrow aspirate confirmed a diagnosis of ALL and she was treated per AALL1131 for high risk ALL which includes the following regimen: Cyclophosphamide 1000 mg/m^2 once per day on days 1 & 29; Cytarabine 75 mg/m^2 on days 1–4, 8 to 11, 29 to 32, 36 to 39; Mercaptopurine 60 mg/m^2 on days 1–14, 29 to 42; Pegaspargase 2500 units/m^2 on days 15 & 43; and Vincristine 1.5 mg/m^2 on days 15, 22, 43, 50. An MRI of the brain obtained as part of her workup revealed hemorrhagic lesion of the corpus callosum, so she was switched to a high-risk protocol including intrathecal methotrexate.

Her first eye examination was performed while the patient was admitted to assess for intraocular involvement given her CNS lesion. Her examination was notable for normal visual behavior and several intraretinal hemorrhages in both eyes consistent with leukemic retinopathy in the setting of thrombocytopenia (platelet count 76). There were no signs of uveitis or leukemic ocular involvement. 2 months after this initial examination, the patient presented with eye pain. Her platelet count had normalized to 236 weeks before presentation. On examination, visual acuity testing was unsuccessful due to lack of patient willingness to engage with acuity testing. IOP was 45 mmHg in the right eye and 16 mmHg in the left eye by applanation tonometry. Anterior chamber slit lamp examination was limited but grossly normal. Posteriorly, the patient was noted to have a complete vitreous hemorrhage in the right eye with no view to the posterior pole and no retinal detachment on B-scan ultrasonography. Dilated fundus examination of the left eye was unremarkable. The presumed diagnosis was ghost cell glaucoma in the setting of vitreous hemorrhage from leukemic retinopathy and the patient was started on maximum topical medical therapy and oral acetazolamide. The IOP in the right eye remained elevated for 3 weeks, thus the patient was referred to a retinal surgeon to perform a vitrectomy with the goal of lowering the IOP. The patient underwent a core vitrectomy in the right eye, though experienced persistent IOP elevation in the month following the procedure, thus was referred for further evaluation and management.

On her initial presentation in our clinic, her best corrected visual acuity was hand motions in the right eye and 20/40 in the left eye by Snellen. IOP was 33 mmHg in the right eye and 15 mmHg in the left eye by iCare tonometry. Examination of the left eye was unremarkable. The right pupil was slightly irregular, dilated, and sluggishly reactive to light. There was a right afferent pupillary defect by reverse. Slit lamp examination revealed lacy iris neovascularization covering 12 clock hours in the right eye (Fig. 1). Gonioscopy was attempted unsuccessfully due to patient cooperation. The patient was phakic with a clear lens. Dilated fundus examination of the right eye revealed residual peripheral vitreous skirt with vitreous hemorrhage as well as retinal vascular attenuation, no obvious foveal light reflex, and a slightly increased cup: disc ratio in the right eye compared to the left eye (Fig. 2A and B). The presumed diagnosis was neovascular glaucoma in the setting of a prior retinal ischemic event leading to vitreous hemorrhage. Given these findings, an examination under anesthesia with fluorescein angiography was recommended.

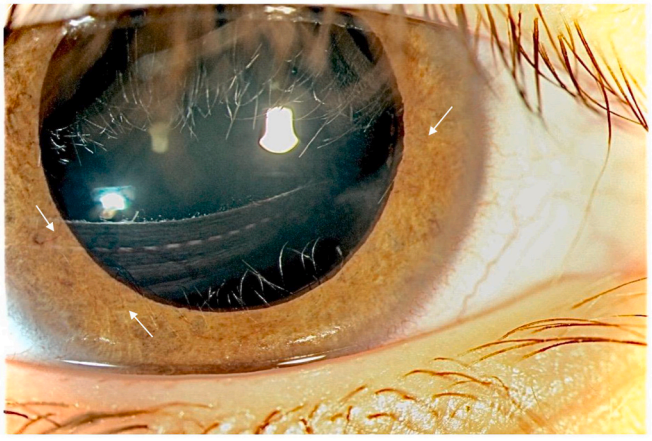

Fig. 1. Right eye indicating dilated pupil as well as extensive iris neovascularization (white arrows).

Under anesthesia, the IOP was 31.5 and 18.0 mmHg by pneumotonometry in the right and left eyes, respectively. Microscope and slit lamp examination confirmed findings of iris neovascularization in the right eye as well as a yellow tint to the anterior chamber (presumed to be dehemoglobinized blood). There was no hyphema and gonioscopy was open to the ciliary body 360° with no neovascularization of the angle. Dilated fundus examination revealed findings similar to those observed in clinic. Optical coherence tomography (OCT) of macula in the right eye demonstrated significant macular edema with subretinal fluid and notable retinal atrophy temporally. OCT of the left eye was unremarkable apart from a trace epiretinal membrane (Fig. 2C and D). Fluorescein angiography was performed following administration of a 7.7 mg/kg bolus of fluorescein. While attempting to obtain transit images of the right eye, there was noted to be a diffuse monotone signal, but no view of the retinal vasculature. Images taken of the left eye during the same time period revealed normal retinal vasculature consistent with the patient's history of mild leukemic retinopathy which had resolved (Fig. 2E and F). External examination of the right eye demonstrated diffuse leakage of fluorescein into the anterior chamber, presumably due to leakage from the iris neovascularization, likely blocking any signal from the posterior pole (Fig. 3). Given these findings, the patient was diagnosed with mixed mechanism glaucoma (neovascular and ghost cell) due to a vitreous hemorrhage in the setting of a presumed prior ischemic event. The patient underwent an intravitreal injection of 1.25 mg in 0.05 mL of bevacizumab in the right eye with the goal of IOP reduction and palliation, an off-label use. An anterior chamber paracentesis was performed, and cytology testing found the sample to be acellular and non-diagnostic. At her post-injection month 1 visit, the vision was hand motions in the right eye and 20/30 in the left eye by Snellen. IOP was 33 mmHg in the right eye and 10 mmHg in the left eye by iCare tonometry. The examination of the right eye was stable with regression of iris neovascularization, and the patient was comfortable with no eye pain. The guarded visual prognosis for the right eye with an afferent pupillary defect and vision that did not improve despite clear media due to extensive macular atrophy was discussed with the main goal of palliation.

3. Discussion

The presentation of a vitreous hemorrhage with IOP elevation in children is rare but requires further workup to determine the etiology and optimal treatment. Fluorescein angiography is often a useful test in this clinical scenario, particularly once the vitreous hemorrhage has cleared. This case demonstrated a rare limitation of fluorescein angiography in the setting of active iris neovascularization.

Compared to adults, the incidence of vitreous hemorrhage in children is low. When present, the most common cause is trauma, which includes penetrating trauma, non-penetrating trauma, and non-accidental trauma or shaken baby syndrome. Spontaneous vitreous hemorrhage has also been described as an etiology in children.[4,5] Patients with a history of retinopathy of prematurity can also present with vitreous hemorrhage either in the acute phase of the disease or delayed.[10] Finally, any systemic condition which predisposes a child to bleeding increases the risk for vitreous hemorrhage.

Ocular complications are relatively common in patients with leukemia, many related to thrombocytopenia from the disease itself or from chemotherapeutic agents.[6,11] In this setting, several factors can contribute to ischemia: ischemia from leukemic retinopathy or direct invasion of tumor cells, or complications like disseminated intravascular coagulation and tumor lysis syndrome which can lead to thrombotic events.[11] Indirectly, the other hematological abnormalities seen in leukemia including thrombocytopenia, hyperviscosity syndrome, and

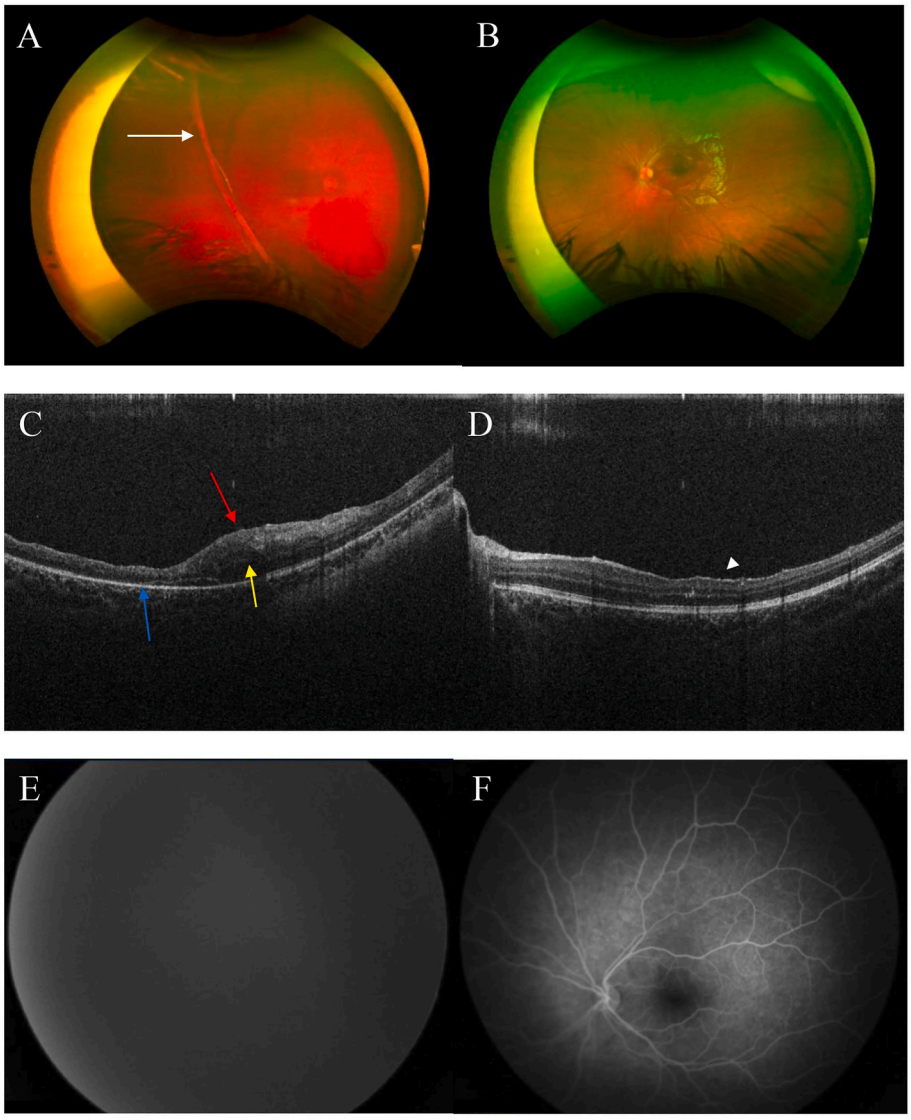

Fig. 2. Multimodal imaging of the right and left eye. Wide-field dilated fundus photography (Optos photographs obtained in clinic are shown instead of Retcam images obtained while the patient was under anesthesia given better image quality) — (A) Right eye indicating residual peripheral vitreous skirt left after vitrectomy (white arrow), retinal vascular attenuation, as well as no obvious foveal light reflex and increased cup:disc ratio compared to left eye; (B) Unremarkable left eye. Optical coherence tomography — (C) Right eye indicating nasal macular edema (red arrow) with subretinal fluid (yellow arrow) and temporal retinal atrophy (blue arrow); (D) Left eye notable for a small epiretinal membrane (white arrowhead) with no other retinal pathology. Fluorescein angiography images captured during the venous laminar phase — (E) Right eye demonstrating diffuse monotone signal and no view of the retinal vasculature; (F) Left eye demonstrating normal retinal vasculature and perfusion.

anemia, can all lead to vitreous hemorrhage.[12] These complications can potentially be further exacerbated by chemotherapeutic agents,[7] which may have contributed to this patient's vitreous hemorrhage.

Neovascular glaucoma, which is caused by an imbalance between pro-angiogenic factors and anti-angiogenic factors from tissue ischemia,[13] is most commonly caused by diabetes mellitus, central retinal vein occlusion, and ocular ischemic syndrome.[14] Ophthalmic examination findings depend on the stage of the disease: early on, the symptoms relate to the primary retinal disease causing the iris neovascularization; then iris neovascularization starts to develop, appearing first as a cluster of vessels on the pupillary border of the iris; followed by more prominent neovascularization and IOP elevation; and finally angle closure occurs with associated eye pain, photophobia, poor vision, and extremely high IOP. Sequelae include cataract formation and phthisis bulbi.[14] In children, neovascular glaucoma is rare and results from either local or systemic causes. Examples of local causes include Coats disease, retinopathy of prematurity, posterior or intermediate uveitis, and retinoblastoma. Systemic causes include neurofibromatosis type 1, von Hippel-Lindau syndrome, systemic lupus erythematosus, and ocular metastases.[15]

By providing information regarding the circulation of the retina, choroid, and other ocular structures, fluorescein angiography is a crucial diagnostic tool to determine the status of retinal and optic nerve vascularization and perfusion.[9] Sodium fluorescein is a small molecular weight molecule and dye which when injected intravenously, travels to the retinal vasculature and emits light after excitation with blue light ultimately creating an image representative of the retinal vasculature. Any media opacity that precludes the view to the retina will interfere with successful angiogram acquisition. Fluorescein leaks out of blood vessels in the setting of pathology associated with increased retinal vessels permeability such as neovascular and ischemic conditions.[16,17] Leakage in the posterior pole typically manifests as abnormal perivascular signal. In the setting of abnormal iris blood vessels, fluorescein leaks rapidly into the anterior chamber mixing with aqueous and

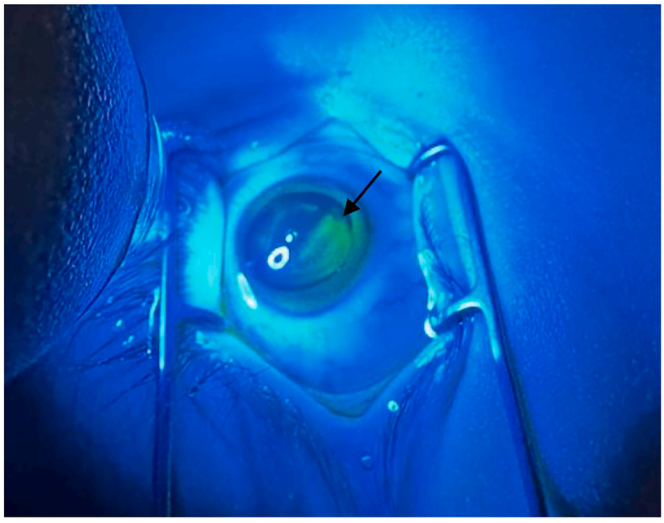

Fig. 3. External photograph of the right eye demonstrating leakage of fluorescein into the anterior chamber (black arrow).

ultimately creating a high intensity signal which prevents successful visualization of posterior pole structures. We present a case of a rare occurrence of fluorescein leakage into the anterior chamber ultimately preventing successful visualization of retinal pathology in a patient with clear media. In our patient, the fluorescein leakage was most likely attributable to pathologic iris neovascularization. In settings where fluorescein angiography cannot be successfully performed, or images cannot be obtained, optical coherence tomography (OCT), OCT angiography, wide-field retinal imaging, and B-scan ultrasonography can help establish the diagnosis.[18] Additionally, fluorescein angiography can be repeated following appropriate management of iris neovascularization.

In the absence of definitive angiographic diagnostic information, our patient was empirically diagnosed with mixed mechanism glaucoma (neovascular and ghost cell) based on the constellation of examination findings. Ghost cell glaucoma is due to obstruction of the trabecular meshwork by 'ghost cells,' which are degenerated red blood cells, after surgical procedures or trauma in patients with vitreous hemorrhage. Vitrectomy, like in our patient, or other procedures or trauma that disrupt the anterior hyaloid membrane, can allow a passageway for damaged red blood cells to reach the anterior chamber of the eye and obstruct the trabecular meshwork, resulting in an elevation of IOP. Occasionally, Heinz bodies (denatured and oxidized hemoglobin which form clumps in red blood cells) can be seen on anterior chamber aspirates, which can be a diagnostic finding for ghost cell glaucoma.[8] However, our anterior chamber aspirate was found to be non-diagnostic, so it did not help contribute to our patient's diagnosis. On the other hand, neovascular glaucoma due to retinal ischemia can also contribute to IOP elevation in patients with vitreous hemorrhage from the angiogenic factors produced that eventually result in neovascular blockage of the trabecular meshwork, leading to markedly increased IOP.[19] In our patient, we have both combining effects leading to a diagnosis of mixed mechanism glaucoma. Given that the patient's IOP was elevated in the setting of maximum medical therapy and extensive non-clearing vitreous hemorrhage, it would have been reasonable to consider earlier vitrectomy, though there is limited data to support timing of this intervention in children.[20]

4. Conclusions

We present a case of anterior chamber fluorescein leakage due to active iris neovascularization in a child with leukemia, vitreous hemorrhage, and neovascular and ghost cell glaucoma. We review considerations for the differential diagnosis and useful diagnostic tests in this clinical scenario.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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