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Case Report

Candy Cane Hypopyon Secondary to Intraocular Mantle Cell Lymphoma: A Case Report

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Abstract

Introduction: Bilateral hemorrhagic hypopyon, also known as candy cane hypopyon, is an extremely rare presentation which we report as a unique case in association with intraocular mantle cell lymphoma (MCL). ***Case Presentation:*** A 63-year-old white male presented with a 3-week history of conjunctival injection OS that was unresponsive to erythromycin ointment and topical steroids, in the setting of recently discovered diffuse lymphadenopathy and malaise. On presentation, he was found to have bilateral hemorrhagic hypopyon. Lymph node biopsy was diagnostic of MCL, and subsequent anterior chamber paracentesis confirmed intraocular MCL. The patient was put into remission with intravitreal rituximab injections, systemic chemotherapy, and external beam radiation. ***Conclusion:*** Cases of MCL with ocular involvement typically involve ocular adnexal structures, and seldom involve the uvea. Furthermore, this patient represents an extremely unusual case in his presentation with a hemorrhagic hypopyon.

Introduction

Hemorrhagic hypopyon, also termed "candy cane hypopyon," is a rare presentation that is due to the mixture of hyphema and hypopyon, as both erythrocytes and neoplastic leukocytes accumulate and layer together in the anterior chamber. Hemorrhagic hypopyon is most commonly associated with infectious causes [1], oftentimes herpetic, but

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there have also been a few reports of hemorrhagic hypopyon associated with neoplasia [2].

Mantle cell lymphoma (MCL) is a rare subtype of B-cell non-Hodgkin lymphoma (NHL) that uncommonly involves the eye, particularly when compared to other lymphomas. The orbit is the most commonly affected site, followed by the eyelids, the lacrimal gland, and conjunctiva [3]. Here, we report a case of a patient who presented with bilateral hemorrhagic hypopyon and extensive lymphadenopathy, which was eventually attributed to systemic and intraocular MCL. 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/10.1159/000541413).

Case Report

A retrospective review of the patient's record was done to obtain data for this case report. This 63-year-old white American male presented to our tertiary uveitis clinic for evaluation of a 3-week history of redness of the left eye (OS) and extensive lymphadenopathy. The patient reported blurring, loss of vision in the left lower quadrant, and supraorbital pain bilaterally (OU), all of which had worsened over the preceding 3 weeks. During the course of these ocular symptoms, the patient also experienced progressive enlargement of his lymph nodes. Symptoms began while he had a viral upper respiratory infection, so they were initially felt to represent viral conjunctivitis. However, given the additional suspicion of bacterial conjunctivitis, the patient was put on a 2-week course of erythromycin ointment by his primary care physician 3 times daily. Despite that, symptoms continued to worsen and he was then referred to an ophthalmologist who, in turn, referred him to our institution. The referring ophthalmologist started him on prednisolone acetate 1% every hour OS, tobramycin/dexamethasone ointment at bedtime OS, and cyclopentolate 1% 3 times per day OS a week prior to the patient's presentation at our clinic. At the time of presentation, the patient was also being worked up for diffuse bilateral lymphadenopathy of the preauricular, submandibular, cervical, supraclavicular, and axillary lymph nodes. He denied any recent fever, chills, weight loss, headache, rashes, or joint pains, though he did endorse a several-week history of malaise.

On examination, the best corrected visual acuity was 20/20 in the right eye (OD) and 20/125 OS. Intraocular pressures were 11 mm Hg OD and 32 mm Hg OS by applanation tonometry. Slit lamp examination showed, in accordance with SUN criteria, 1+ cell OD, 4+ cell OS, and a gelatinous, layered hypopyon with RBC layering OU, indicative of a hemorrhagic hypopyon (Fig. 1a, b). On dilated examination, 1+ vitreous haze and slight optic nerve pallor were noted through an extremely hazy view OS, with no pathology noted OD. Fluorescein angiography was not attempted due to the lack of clear view OS. B scan showed no retinal detachment or identifiable masses OU. The patient was diagnosed with panuveitis, with malignancy or infectious etiologies strongly suspected. An anterior chamber paracentesis (AC tap) was performed OS after sterilization with povidone iodine, and anesthetization with proparacaine and tetracaine, in a minor procedure room of our outpatient clinic using a 30-g unfiltered hypodermic needle and a 1cc syringe. However, this yielded only acellular, dense, proteinaceous material. He was prescribed oral prednisone 60 mg daily and prednisolone 0.1% drops 3 times a day in both eyes (OU), brimonidine tartrate/timolol maleate ophthalmic solution twice per day OS, travoprost daily OS, and brinzolamide 3 times per day OS to manage his significant inflammation and elevated intraocular pressure OS.

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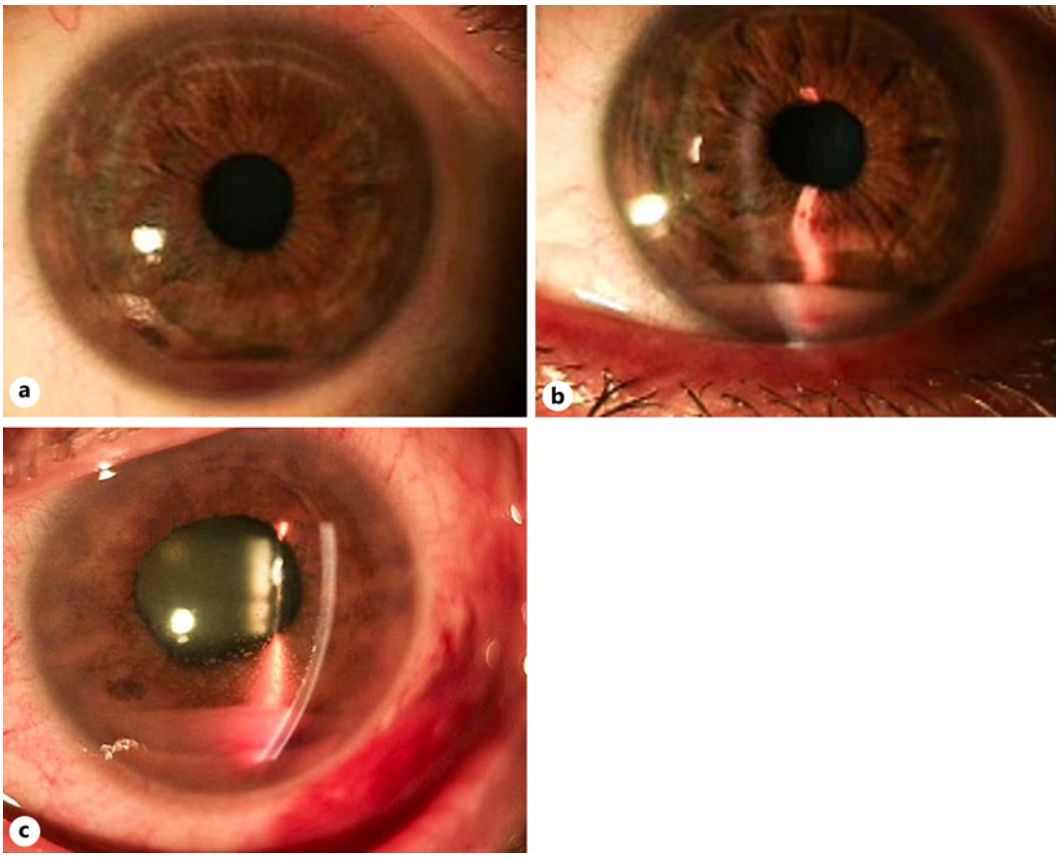

Fig. 1. External photography OU: external photographs of initial presentation OD (**a**) and initial presentation OS (**b**) revealing hemorrhagic hypopyon OU, though more prominent OS, with notable layering of both erythrocytes and neoplastic leukocytes. **c** External photographs of worsening hemorrhagic hypopyon OS.

The patient was urgently admitted to the hospital to undergo thorough testing and lymph node biopsy, with submental lymph node biopsy showing evidence of MCL. Lumbar puncture revealed lymphocytes and monocytes in the cerebrospinal fluid, though no organisms were seen in the CSF or blood. Human immunodeficiency virus, syphilis serology, and hepatitis panels were all negative. Positron emission tomography-computerized tomography revealed bilateral cervical, mediastinal, axillary, inguinal lymph nodal, and splenic fluorodeoxyglucose uptake compatible with lymphoma (Fig. 2d). Magnetic resonance imaging revealed extensive marrow signal abnormality but no orbital involvement was seen (Fig. 2a–c). After discharge from the hospital, a pars plana vitrectomy OS was scheduled to collect a tissue biopsy prior to starting a CNS-grade chemotherapy regimen. Vitreous biopsy results were negative for cellular atypia, IgH rearrangement, bacterial cultures, fungal cultures, and polymerase chain reaction for cytomegalovirus, herpes simplex virus 1 and 2 (HSV-1/2), Epstein-Barr virus, varicella zoster virus, and Toxoplasma gondii.

Two weeks after his initial presentation, the hemorrhagic hypopyon significantly worsened OD (Fig. 1c) and gonioscopy revealed small lumps along the iris inferiorly OD which indicated iris involvement. Fluorescein angiography showed an overall mottled pattern OU (Fig. 3a–d) and indocyanine green angiography revealed nonspecific hypocyanescent spots OU. B scan showed vitreous debris in the posterior chamber OS indicating posterior

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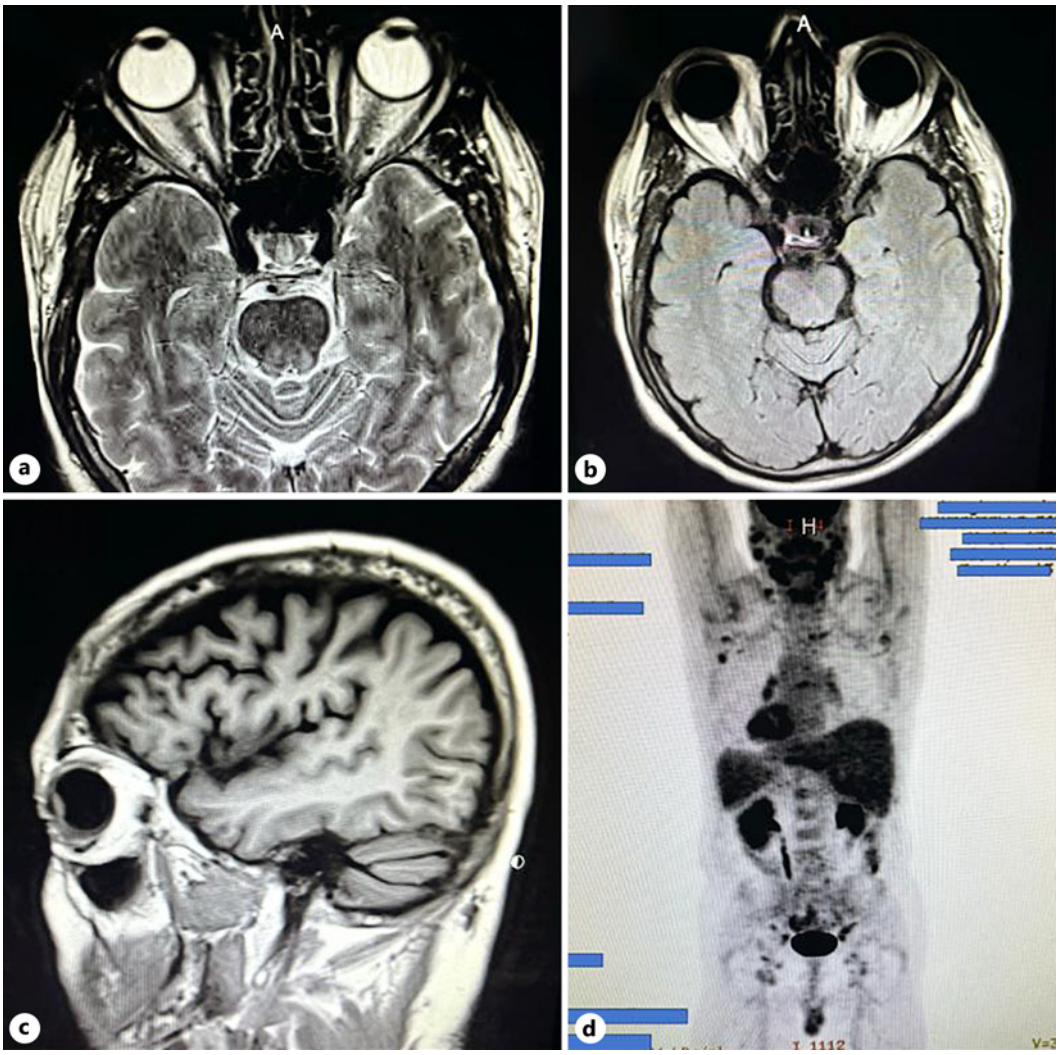

Fig. 2. Magnetic resonance imaging (MRI) and positron emission tomography scan. MRI of the brain and orbits showing extensive marrow signal abnormality with no focal nodularity or mass in the orbit. **a** Axial T2 weighted image without contrast. **b** Axial T1 weighted image without contrast. **c** Sagittal T1 weighted image with 10 mL gadobutrol contrast. **d** PET scan showing bilateral cervical, mediastinal, axillary, inguinal lymph nodal, and splenic fluorodeoxyglucose uptake with maximum standardized uptake values ranging between 2 and 3.

involvement. At this point, given the previously negative intraocular fluid analyses, worsening inflammation, and strong suspicion of intraocular lymphoma, the patient was started on empiric weekly intravitreal injections of rituximab 1 mg OU, with an AC tap done at the time of the first injection in each eye. The resultant aqueous biopsy was positive for malignant lymphomatous cells OU, consistent with MCL by cytopathology and flow cytometry studies. Given the suspicion of a false-negative result with the initial vitreous biopsy, the rarity of mantle cell involvement in the anterior chamber, the strong association of hemorrhagic hypopyon with infectious causes, and to potentially rule out a superimposing infection, we repeated an infectious panel on the AC tap specimen. The aqueous biopsy was negative for bacterial cultures, fungal and viral polymerase chain reaction studies for HSV-1/2, cytomegalovirus, Epstein-Barr virus, and varicella zoster virus. This indicated that the hemorrhagic hypopyon was in fact a hypopyon due to the presence of neoplastic cells in the AC.

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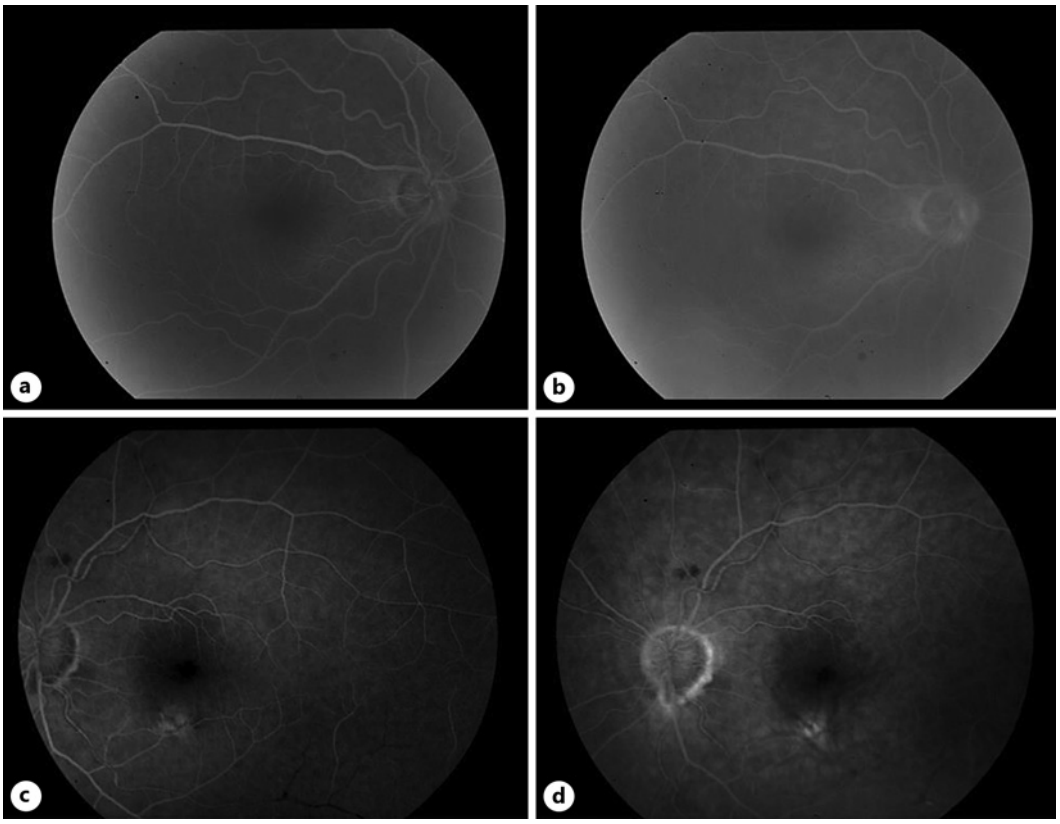

Fig. 3. Fluorescein angiography OU: fluorescein angiography 2 weeks after presentation at 0:57 min OD (**a**), 03:06 min OD (**b**), 01:05 min OS (**c**), 02:50 min OS (**d**).

Table 1. Summary of differential diagnoses for hemorrhagic hypopyon

Diagnosis	Reference
Herpes uveitis, B-cell lymphoma	Winegarner et al. [2] (2017)
VZV +, HIV +	Biswas et al. [1] (2000)
Herpes zoster ophthalmicus	Katherine et al. [6] (2020)
Klebsiella pneumonia	Chao et al. [7] (2009)
Serratia	Al Hazzaa et al. [8] (1992)
Listeria	Alkatan et al. [9] (2014)

List of differential diagnoses for hemorrhagic hypopyon found in the literature along with their references.
VZV, varicella zoster virus.

He was managed with a total of 4 weekly rituximab 1 mg intravitreal injections OU. After the 4th injection, intravitreal bevacizumab 1.25 mg/0.05 mL was given OS due to the development of neovascularization of the iris with worsening of his hyphema OS. He was also provided with systemic chemotherapy (three cycles of bendamustine-rituximab and three cycles of cytosine arabinoside (Ara-C)-rituximab) as well as two cycles of external beam radiotherapy. The hemorrhagic hypopyon improved with the systemic chemotherapy and external beam radiotherapy and the patient's hemorrhagic hypopyon completely resolved.

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The patient received autologous bone marrow stem cell transplantation with carmustine-etoposide-cytarabine-melphalan conditioning (also known as BEAM conditioning) later that year. The conditioning regimen received included carmustine 300 mg/m^2 on day 6 prior to the stem cell infusion (SCI), etoposide 200 mg/m^2 on days 5, 4, 3, and 2 prior to SCI, Ara-C 200 mg/m^2 intravenously q12 h on days 5, 4, 3, and 2 prior to SCI, melphalan 140 mg/m^2 on the day before SCI, and granulocyte stimulating factor 5 μg/mg daily starting on day 5 after SCI until the absolute neutrophil count was more than 500. The patient recovered well from his bone marrow stem cell transplantation. He experienced recurrence of ocular neoplastic infiltration OS 1 year later, which completely resolved with 4 weekly intravitreal injections of rituximab 1 mg OS. After this recurrence, the patient's intraocular and systemic MCL went into remission and has not recurred as of 7 years from the initial presentation.

Discussion

MCL is a rare type of aggressive B-cell NHL that represents about 9% of all adult-onset NHL [4]. The orbit is involved in 8% of all extranodal lymphomas, but only in 1–5% of extranodal MCL [5]. Hemorrhagic, or candy cane, hypopyon, which is the layering of hyphema and hypopyon in the anterior chamber, is a rare manifestation seen primarily in uveitis of infectious etiology [1] but has also been seen in non-infectious cases, as well as in leukemia and intravascular lymphoma [2]. Table 1 summarizes the differential diagnosis and current published case reports on hemorrhagic hypopyon [1, 2, 6–9].

The earliest literature describing hemorrhagic hypopyons dates back to 1976 in a case report by Bonner et al. [10] They described a case of hemorrhagic hypopyon which was discovered to be caused by chronic lymphoid leukemia. Intravascular lymphomas have been associated with various ocular manifestations, including pseudo-hypopyon, hypopyon, and hyphema [2]. However, most hemorrhagic hypopyons are usually associated with an infectious process, especially viral infections (see Table 1). One case of hemorrhagic hypopyon associated with herpes simplex virus uveitis and intravascular lymphoma speculated that both HSV infection and underlying intravascular lymphoma contributed to this rare manifestation. They speculated that the increased vascular permeability, dilation, and damage to blood vessels observed with intravascular lymphomas contributed to the hypopyon formation through inflammatory cell leakage into the AC and that the HSV-associated uveitis likely contributed to the formation of the hyphema layer [2].

To the best of our knowledge, this is the first case of hemorrhagic hypopyon proven by aqueous humor sampling to be seen in relation to intraocular MCL. Reported cases of MCL metastasis with ocular involvement have most commonly involved the ocular adnexal structures such as the eyelid, lacrimal glands [5], conjunctiva [11], and orbital tissue [3]. Uveal involvement has rarely been reported, with none of these cases presenting with a hemorrhagic hypopyon [11–15].

Statement of Ethics

This study was approved by the WCG Institutional Review Board (IRB tracking number: 120160012). Written informed consent was obtained from 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

F.B.: study conceptualization and design, analysis and interpretation of the results, literature review, led manuscript composition, final manuscript preparation, and writing and manuscript editing. A.Z. and P.R.: study design, analysis and interpretation of the results, literature review, and manuscript composition. A.M.P.: study conceptualization and design, literature review, and manuscript composition. T.V. and Y.M.: literature review, manuscript composition and revision, and final manuscript preparation. S.D.A.: study conceptualization and design, performed clinical examination and analysis of referenced case, final manuscript preparation, and analysis and interpretations of the results. C.S.F.: study conceptualization and design, performed clinical examination and analysis of referenced case, and analysis and interpretations of the results.

Data Availability Statement

All relevant clinical data analyzed during this study are included in this case report. Further inquiries can be directed to the corresponding author.

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