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Case Report

Bilateral Cystoid Macular Edema with Zanubrutinib Therapy: A Case Report

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Keywords
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Abstract
We present a patient with recurrent mantle cell lymphoma (MCL) who was treated with zanubrutinib, a Bruton's tyrosine kinase inhibitor. He subsequently developed bilateral cystoid macular edema (CME) in both eyes. This is the first report of CME in a patient with MCL who was treated with zanubrutinib. CME was refractory to topical corticosteroid therapy, but sub-Tenon's steroid injections and holding off zanubrutinib managed to decrease the CME. Treatment managed to prevent further vision loss but did not restore lost vision. The prompt ophthalmic exam is recommended for patients on zanubrutinib with decreased vision.

Introduction

Mantle cell lymphoma (MCL) is a rare subtype of B-cell non-Hodgkin lymphoma. The annual incidence of MCL is one case per 200,000 people in the USA [1]. Treatment of MCL is dependent upon stage and cytogenetics of the cancer, health of the patient, and goals of care. Treatment strategies include observation, radiotherapy, chemotherapeutic regimens, or targeted cell therapy, followed by autologous stem cell transplantation, with ensuing maintenance therapy or salvage regimens based on treatment response [2].

Bruton's tyrosine kinase (BTK) is a tyrosine kinase that is integral in the signal transduction of B-cell antigen receptors, which drive the proliferation of normal and malignant B cells [3]. BTK inhibitors, such as zanubrutinib, are effective targeted therapy medications. They became a mainstay in the treatment of B-cell malignancies, demonstrating durable efficacy in relapsed or refractory MCL [4, 5].

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Side effects of BTK inhibitors include bleeding, atrial fibrillation, arthralgia, infection, diarrhea, and hypertension [6]. The RESONATE trial demonstrated that of 195 patients taking ibrutinib for treatment of chronic lymphocytic leukemia (CLL), 19 (10%) experienced blurred vision compared to 6 (3%) in the ofatumumab group, but the authors did not offer an explanation for the blurry vision [7]. The final analysis from the RESONATE trial revealed that 32 (16%) of the 195 patients had to discontinue ibrutinib due to adverse events [8]. A preclinical study demonstrated that ibrutinib rapidly crosses the blood-brain barrier after administration. In an observational study, ibrutinib was found to successfully treat MCL central nervous system dissemination in 3 patients, which indicated the potential of central nervous system side effects [9, 10].

Here, we present the first described case of cystoid macular edema (CME) in an MCL patient that occurred following zanubrutinib use. This patient's CME improved after discontinuation of zanubrutinib and administration of sub-Tenon's corticosteroids.

Case Report

We present an 84-year-old male who was diagnosed with MCL in July 2012. The patient initially opted for observation of his malignancy. Six months following his initial diagnosis, the patient presented to the hospital with dyspnea. Imaging studies revealed lymphadenopathy in his mediastinum and right pleural effusion. He was subsequently treated with 4 cycles of bendamustine and rituximab followed by radiation, which achieved remission. In late 2019, he noted a swelling on the roof of his mouth. Oral lesion biopsy was consistent with recurrence of MCL. Whole-body PET scan revealed a right retrobulbar mass and multiple abdominal masses. In February 2020, he was started on ibrutinib 560 mg daily by the hematology oncology team. PET scan in September 2020 demonstrated complete resolution of all areas of lymphadenopathy. Shortly after, in October 2020, ibrutinib was reduced to 420 mg due to increasing fatigue, dysuria, and a urinary tract infection that were all attributed to ibrutinib. In May 2021, the patient was switched from ibrutinib 420 mg to zanubrutinib 80 mg BID due to persistent urinary symptoms.

One week after starting zanubrutinib, the patient reported progressively blurred vision. He was diagnosed with CME in his left eye (OS) and was started on difluprednate eye drops QID OS. Four weeks later, the patient reported that his vision deteriorated, and he did not feel safe to drive. He was referred to the retina service at that point. The patient's past ocular history was significant for severe glaucoma post glaucoma drainage implants in both eyes (OU), Fuch's endothelial dystrophy post Descemet's stripping endothelial automated keratoplasty OU, and cataract extraction with lens implants OU.

On presentation to the retina service, the patient had a visual acuity (VA) of 20/100 in the right eye (OD) and 20/50 OS and an intraocular pressure (IOP) of 12 mm Hg OD and 15 mm Hg OS. There were no anterior chamber cells or flare on the slit-lamp exam. The refractive media was clear with no vitritis. The ocular fundus exam revealed glaucomatous optic nerve head OU and dull foveal reflex OS. Optical coherence tomography (OCT) showed non-center involving CME OD and center involving CME with foveal distortion OS refractory to topical difluprednate drops (Fig. 1a). The patient received sub-Tenon's triamcinolone acetonide 40 mg/mL injection OS. In June 2021, the patient presented with VA of 20/60 OS and IOP of 13 mm Hg OS. OCT revealed persistent CME OD and improved CME OS (Fig. 1b). After discussion with the treating oncologist and the patient, zanubrutinib was placed on hold due to blurred vision.

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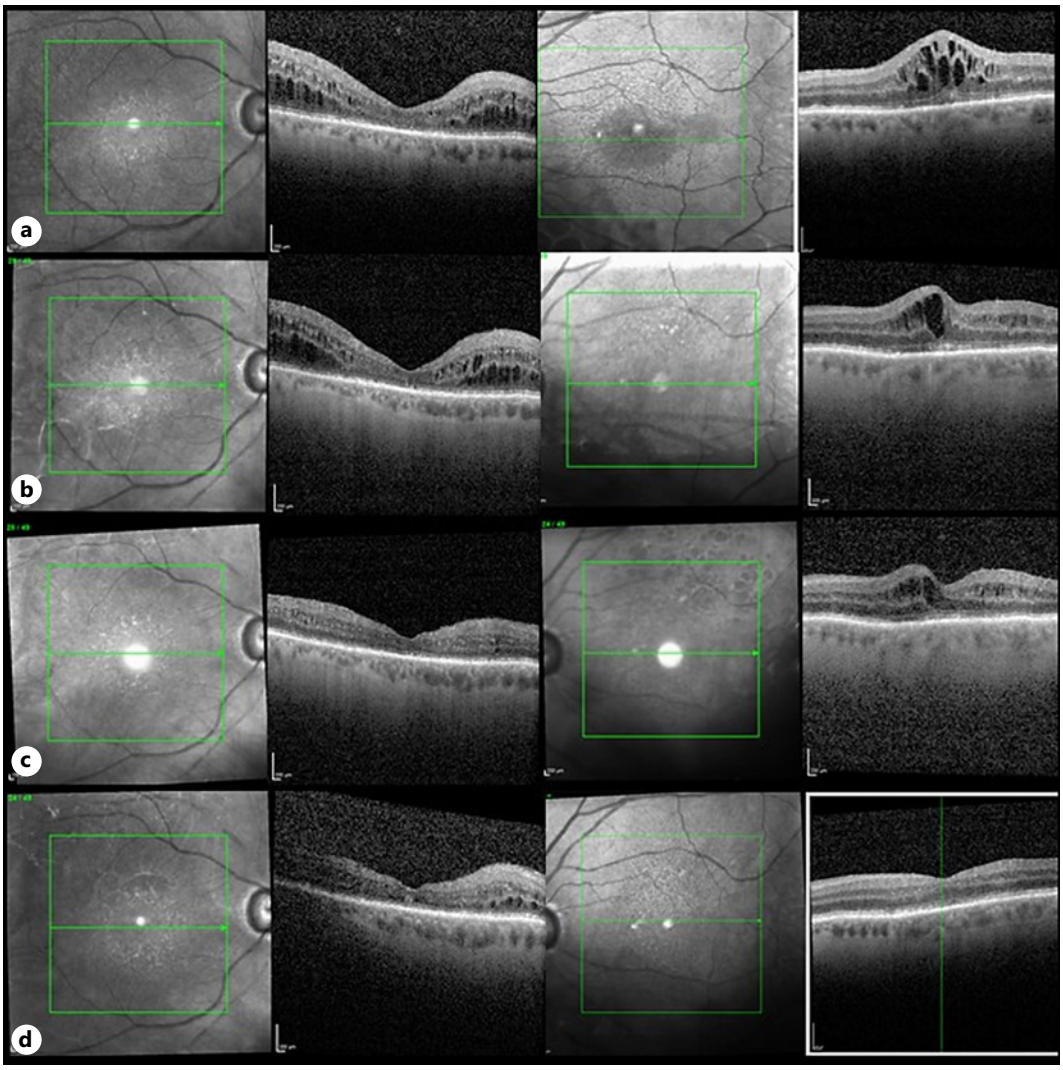

Fig. 1. Optical coherence tomography (OCT) scans. OCT scans showing bilateral macular edema on the initial visit (**a**). Persistent macular edema OD and decreased edema after sub-Tenon's triamcinolone acetonide 40 mg/mL injection OS (**b**). Decreased edema OU after cessation of zanubrutinib (**c**). One-year follow-up OCT showing mild increase in edema OD and resorbed edema OS (**d**).

In July 2021, the patient presented with VA of 20/125 OD and 20/50 OS and IOP of 10 mm Hg OD and 14 mm Hg OS. OCT was remarkable for decreased CME OS (Fig. 1c). The patient continued to receive sub-Tenon's injections over the following 10 months.

At the patient's most recent follow-up in August 2022, he presented with a VA of 20/125 OD and 20/50 OS and IOP of 12 mm Hg OD and 27 mm Hg OS. OCT revealed mild CME OD and resolved CME OS (Fig. 1d).

Discussion

In summary, we present a case of bilateral CME associated with zanubrutinib in a patient treated for MCL. This is the first described case of CME after use of zanubrutinib in MCL. Unique to this case is that the patient's CME was resistant to topical therapy which required

sub-Tenon's corticosteroids and cessation of zanubrutinib. In addition, this case demonstrated that early detection and treatment of macular side effects helped prevent further vision loss and did not restore lost vision.

CME has previously been reported in CLL patients receiving ibrutinib (BTK family). The first CLL patient was treated with ibrutinib for 4 weeks for relapsing CLL and began experiencing blurry vision. This patient was treated with topical dexamethasone 0.1% QID and with ketorolac 0.5% TID. After 6 weeks of treatment, the patient experienced complete resolution of CME without altering the dose of ibrutinib [11]. The second patient was treated with ibrutinib for 4 years for relapsing CLL and began to experience blurry vision. This patient experienced transient improvement with the reduction of his dose to 140 mg, but then his vision again declined. Following this, the patient received grid laser, and ibrutinib was discontinued with complete resolution of CME [12].

CME is characterized by the accumulation of cystic like spaces in the neurosensory retina, often in the inner nuclear layer and outer plexiform layer of Henle [13]. Typically, CME is self-limiting, with most patients eventually returning to their previous baseline VA [14]. In this particular case, the patient's CME did not regress with the sub-Tenon's corticosteroid injections while on a BTK inhibitor. Since improvement was not observed on OCT after the first corticosteroid injection in the left eye, we hypothesized that discontinuation of the BTK inhibitor may decrease the patient's ocular pathology (Fig. 1c).

Zanubrutinib has also been described to treat vitreoretinal lymphoma, a rare intraocular malignancy. Wang et al. [15] described three cases of vitreoretinal lymphoma being effectively treated with zanubrutinib to complete remission. However, use of zanubrutinib to treat vitreoretinal lymphoma is not without risk as a case report described bilateral vitreous hemorrhage after the fourth administration of intravitreal methotrexate combined with paracentesis in a patient taking zanubrutinib. This case report noted that after discontinuation of zanubrutinib, the hemorrhage resolved with vitrectomy in the left eye and without intervention in the right eye [16].

Overall, ocular side effects are rare in targeted therapy but still should be monitored by the patient's oncologist and eyecare provider. Checkpoint inhibitors, another type of targeted therapy, are known to cause dry eye, uveitis, and myasthenia gravis with ocular involvement [17]. Treatment of chorioretinal inflammation is typically achieved by using a combination of topical drops, ocular injections, and systemic steroids [18]. BTK inhibitors have less widely reported ocular side effects; however, management of ocular side effects may be needed. Local administration of corticosteroids allows for effective drug delivery to the eye and limits systemic side effects [19]. However, if the patient has persistent inflammation, it may be necessary to consider systemic alternatives. As a last resort, and with careful collaboration with the patient's oncologist, discontinuation of the tyrosine kinase inhibitor can be considered.

Conclusion

This is the first report of CME secondary to zanubrutinib therapy. Local steroids and holding zanubrutinib decreased the CME. Treatment managed to stabilize vision but did not restore lost vision. This case highlights the importance of prompt ophthalmic examination for decreased vision with zanubrutinib therapy. Close collaboration between oncology and ophthalmology teams is essential for similar patients' treatment. 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/10.1159/000529069).

Statement of Ethics

This study was approved by the Institutional Review Board of the University of Kansas Medical Center (approval number: 00145360). 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

All authors do not have any conflict of interest in the study.

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Author Contributions

Dante Pennipede: manuscript draft. Harrison Sciulli and Radwan Ajlan: manuscript edits and revisions.

Data Availability Statement

All data used in this report can be found within the report. If the editors or anyone else requires additional data, please contact the corresponding author.

References

1 Lynch DT, Koya S, Acharya U. Mantle cell lymphoma. Treasure Island (FL): StatPearls; 2022.
2 Silkenstedt E, Linton K, Dreyling M. Mantle cell lymphoma: advances in molecular biology, prognostication and treatment approaches. Br J Haematol. 2021;195(2):162–73.
3 Burger JA. Bruton tyrosine kinase inhibitors: present and future. Cancer J. 2019;25(6):386–93.
4 Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. Mol Cancer. 2018;17(1):57.
5 Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507–16.
6 Lipsky A, Lamanna N. Managing toxicities of Bruton tyrosine kinase inhibitors. Hematology Am Soc Hematol Educ Program. 2020;2020(1):336–45.
7 Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371(3):213–23.
8 Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol. 2019;94(12):1353–63.
9 Bernard S, Goldwirt L, Amorim S, Brice P, Briere J, de Kerviler E, et al. Activity of ibrutinib in mantle cell lymphoma patients with central nervous system relapse. Blood. 2015;126(14):1695–8.
10 Goldwirt L, Beccaria K, Ple A, Sauvageon H, Mourah S. Ibrutinib brain distribution: a preclinical study. Cancer Chemother Pharmacol. 2018;81(4):783–9.
11 Mirgh SP, Ahmed R, Agrawal N, Bothra S, Mohan B, Garg A, et al. Knowing the flip side of the coin: ibrutinib associated cystoid macular edema. Indian J Hematol Blood Transfus. 2020;36(1):208–10.
12 Saenz-de-Viteri M, Cudrnak T. Bilateral cystoid macular edema in a patient with chronic lymphocytic leukemia treated with ibrutinib. Leuk Lymphoma. 2019;60(3):842–4.
13 Chung YR, Kim YH, Lee SY, Byeon HE, Lee K. Insights into the pathogenesis of cystoid macular edema: leukostasis and related cytokines. Int J Ophthalmol. 2019;12(7):1202–8.

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DOI: 10.1159/000529069

14 Rotsos TG, Moschos MM. Cystoid macular edema. Clin Ophthalmol. 2008;2(4):919–30.
15 Wang L, Guan W, Peng X. Targeting Bruton tyrosine kinase with zanubrutinib for treatment of vitreoretinal lymphoma: report of 3 cases. Front Oncol. 2021;11:676792.
16 Zhang X, Dai R, Zhao C, Zhang M. Case report: intraocular hemorrhage in a primary vitreoretinal lymphoma patient treated with zanubrutinib. Front Med. 2022;9:833565.
17 Dalvin LA, Shields CL, Orloff M, Sato T, Shields JA. Checkpoint inhibitor immune therapy: systemic indications and ophthalmic side effects. Retina. 2018;38(6):1063–78.
18 Davis ME, Francis JH. Cancer therapy with checkpoint inhibitors: establishing a role for ophthalmology. Semin Oncol Nurs. 2017;33(4):415–24.
19 Fung AT, Tran T, Lim LL, Samarawickrama C, Arnold J, Gillies M, et al. Local delivery of corticosteroids in clinical ophthalmology: a review. Clin Exp Ophthalmol. 2020;48(3):366–401.