American Journal of Ophthalmology Case Reports 22 (2021) 101079

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Acute bilateral angle closure induced by monoclonal antibody (Daratumumab) infusion

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ARTICLE INFO

Keywords:
Bilateral angle closure glaucoma
Drug induce angle closure glaucoma
Daratumumab
Monoclonal antibody
Multiple myeloma

ABSTRACT

Purpose: To report a case of daratumumab-induced bilateral angle closure glaucoma and myopia that showed no recurrence after repeated drug administration with prophylactic cycloplegia.

Observations: A 63-year-old man with relapsing multiple myeloma presented with acute bilateral eye pain and blurred vision 14 hours after first daratumumab infusion. Eye examination revealed raised intraocular pressure and shallow anterior chamber. Anterior segment ocular coherence tomography and ultrasound biomicroscopy showed ciliochoroidal effusions in both eyes. The diagnosis of bilateral acute angle closure glaucoma and induced myopia was made. Cycloplegia- and intraocular-pressure-lowering medications were given, which gradually deepened the anterior chambers and normalized intraocular pressure and refraction. The ciliochoroidal effusions completely resolved on day 14. The cycloplegic was given as a premedication for subsequent infusions. There was no recurrence of effusion throughout his 6-month daratumumab treatment course.

Conclusions and importance: Daratumumab can induce ciliochoroidal effusion, which results in acute secondary angle closure and myopia. The potential prophylactic effect of the cycloplegic drug may enable continuation of daratumumab infusion under close monitoring.

Introduction

Daratumumab (Darzalex, Janssen, Biotech, Horsham, PA) is a human anti-CD38 monoclonal antibody that is used to treat multiple myeloma. It was approved by the United States Food and Drug Administration in 2015.[1] Recently, daratumumab has been reported by Lee et al. and Edwards et al. to cause ciliochoroidal effusion and acute angle closure glaucoma.[2,3] Here, we report another case of daratumumab-induced bilateral angle closure; however, our case did not show any recurrence of glaucoma episode after continuing the infusion of monoclonal antibody with prophylactic cycloplegia.

Case report

A 63-year-old man with relapsing multiple myeloma and cast nephropathy was scheduled for 16 mg/kg/week daratumumab administration during the first 8 weeks of treatment and received dexamethasone 20 mg, chlorpheniramine 10 mg and acetaminophen 1000 mg as premedication to prevent infusion-related reactions (IRRs). He presented with acute bilateral eye pain with raised intraocular pressure (IOP) up to 50 mmHg on both eyes, 14 hours after his first daratumumab infusion. His visual acuity was 20/160 in the right eye and 20/200 in the left eye. The refraction was −1.75 diopter in the right eye and −2.50 diopter in the left eye, demonstrating myopic shifts from his prior measurement of −0.50 diopter in both eyes 9 months earlier. Visual acuity after correcting the refractive error was 20/25 in both eyes. The eye examination revealed corneal microscopic cystic edema, diffuse conjunctival chemosis with mild injection and shallow anterior chamber without iris bombe appearance. Both eyes were pseudophakic. Dynamic gonioscopy showed 360° of angle closure (Shaffer grade 0) without peripheral anterior synechiae in either eye. There was no evidence of neovascularization of the angle. Anterior segment optical

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https://doi.org/10.1016/j.ajoc.2021.101079
Received 20 January 2021; Received in revised form 21 March 2021; Accepted 22 March 2021
Available online 26 March 2021

coherence tomography (AS-OCT) and ultrasound biomicroscopy (UBM) showed 360-degree bilateral ciliochoroidal effusion (Figs. 1 and 2). On the fundus examination, the optic nerves appeared pink with a cup to disc ratio of 0.3 in both eyes.

Bilateral drug-induced acute angle closure glaucoma was diagnosed and the patient was prescribed 1% atropine eyedrop twice a day to both eyes along with topical IOP-lowering medications (0.5% timolol maleate eyedrop twice a day, 0.15% brimonidine tartrate eyedrop three times a day, 2% dorzolamide hydrochloride eyedrop three times a day and 0.01% bimatoprost eyedrop once a day). Oral glycerin (1 g/kg) and acetazolamide (250 mg) every 6 hours were also prescribed and subsequently tapered off at day 3. Both oral medications were discontinued at day 4. Serial examinations showed gradual deepening of the anterior chamber and decrease of suprachoroidal fluid (Figs. 3 and 4). At day 7, the visual acuity returned to 20/20 and refraction was +0.50 diopter in both eyes. His IOP was 8 mmHg on both eyes. The topical medications were reduced to 1% atropine, 0.5% timolol and 0.01% bimatoprost eyedrops. Given his very limited cancer treatment options, after an extensive discussion with hemato-oncologists, the patient decided to continue with the second infusion at day 7 per the weekly-scheduled cancer regimen. AS-OCT and UBM were performed 12 hours prior to the second infusion. The results showed a wide angle in both eyes with minimal suprachoroidal collection in all quadrants of both eyes. Without discontinuation of 1% atropine twice daily, the patient showed no sign of recurrent angle closure after the second infusion. There was no worsening of the suprachoroidal fluid detected using AS-OCT on the first day after the second infusion (day 8 after the first infusion; Fig. 4). His IOPs were normalized (ranging between 10 and 12 mmHg) and IOP-lowering medications were completely discontinued on day 9. AS-OCT revealed the complete resolution of the suprachoroidal fluid on day 14 (Fig. 4). It should be noted that he also received high filter hemodialysis on days 5, 6 and 8 (6 hours after the second daratumumab infusion) because of his nephropathy.

The patient was administered daratumumab weekly during the first 8 weeks followed by every 2 weeks for the following 16 weeks and monthly thereafter. Throughout the infusion course, his cast nephropathy was improved without the need for additional hemodialysis. The IOP was checked periodically and stabilized without glaucoma medications. The cycloplegia ceased upon completion of the fourth daratumumab infusion. From the fifth infusion onwards, 1% atropine was given one day prior to infusion and discontinued the day after the infusion. The patient completed the first 6 months of the treatment regimen comprising 16 infusions with no recurrence of the angle closure. At 6 months, his vision was 20/20 in both eyes and the IOP was 12 and 13 mmHg in the right and left eye, respectively.

Discussion

Acute angle closure or acute angle closure glaucoma can occur as an adverse drug reaction of some topical and systemic medications. The mechanism of drug-induced acute angle closure can be divided into pupillary block and non-pupillary block. Pupillary block drug-induced acute angle closure mostly occurs in patients with an anatomical predisposition to angle closure. The medications that cause pupillary dilation, either through sympathetic activation or parasympathetic inhibition, can precipitate pupillary block in these susceptible eyes.[4] Conversely, non-pupillary block drug-induced acute angle closure can occur in a more idiosyncratic pattern, regardless of the eyes' baseline angle status. The mechanisms of non-pupillary block drug-induced acute angle closure can involve lens thickening and forward movement, ciliary body rotation and ciliochoroidal effusion.[5] Several medications have been reported to cause this type of drug-induced angle closure, most of which are sulfonamide derivatives such as topiramate, acetazolamide, methazolamide, indapamide and hydrochlorothiazide.[6] Other

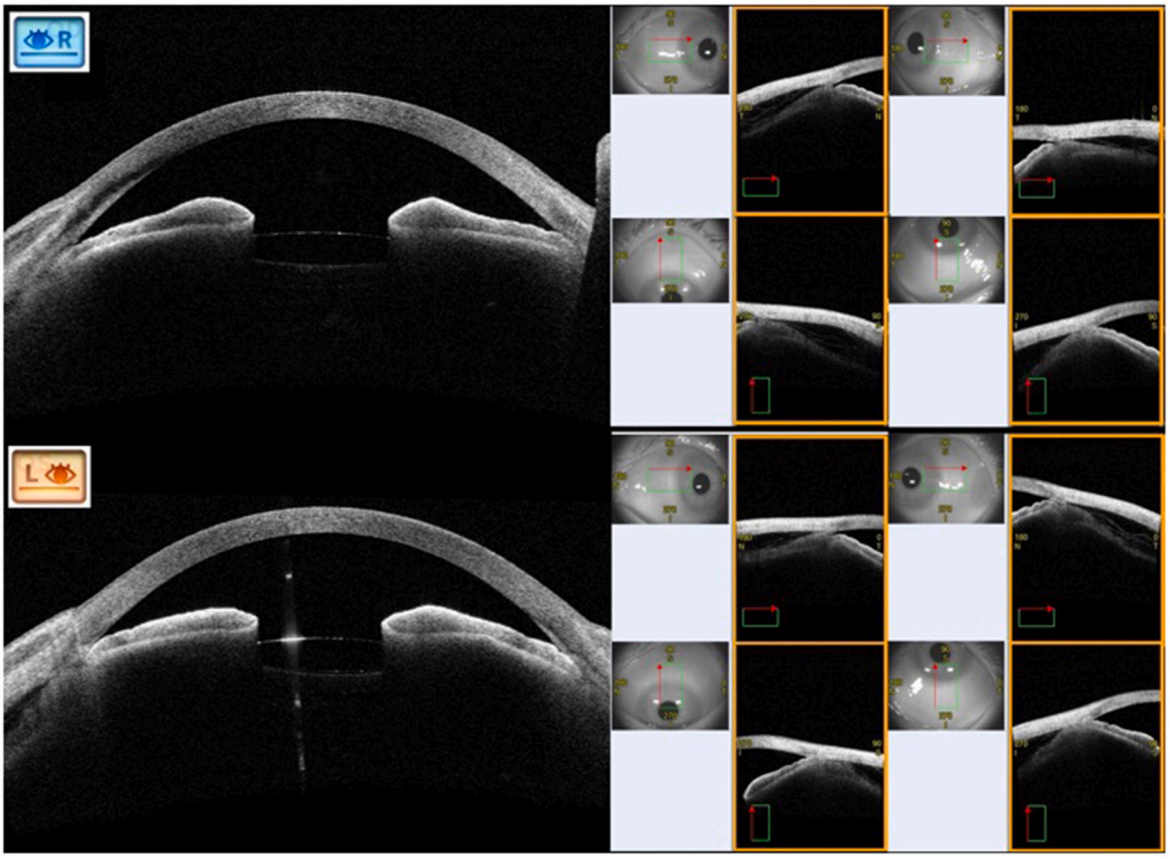

Fig. 1. Anterior segment optical coherence tomography shows angle closure and ciliochoroidal effusion in both eyes.

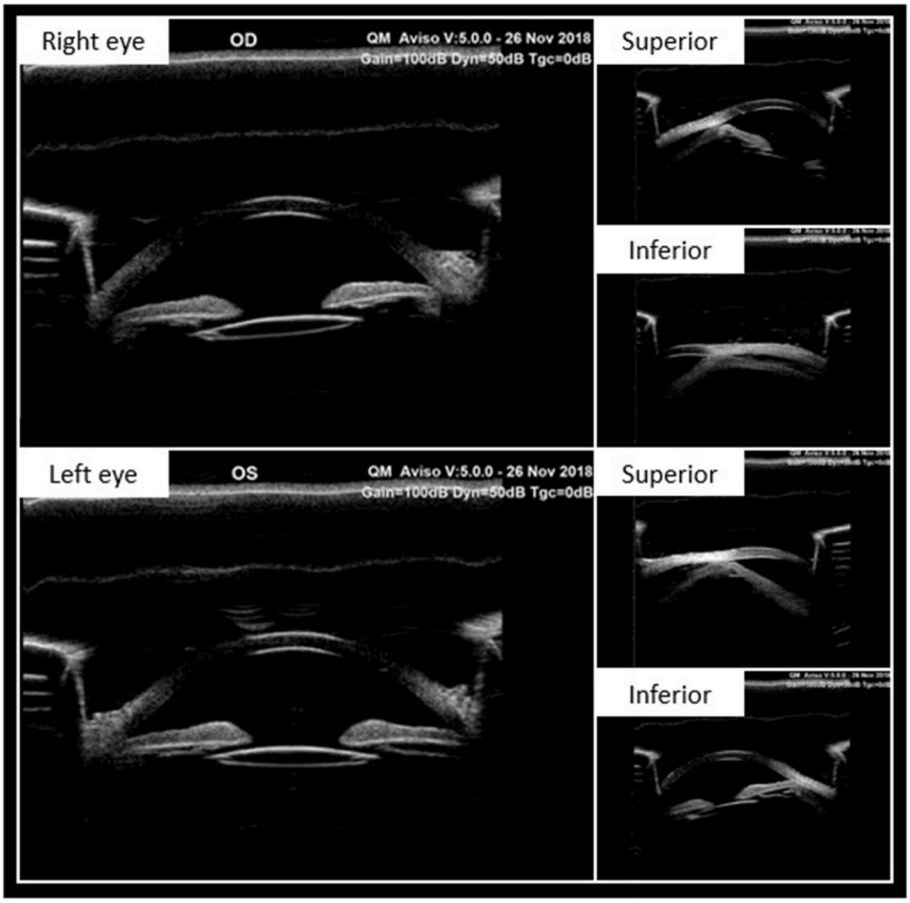

Fig. 2. Ultrasound biomicroscopy shows angle closure and ciliochoroidal effusion in both eyes.

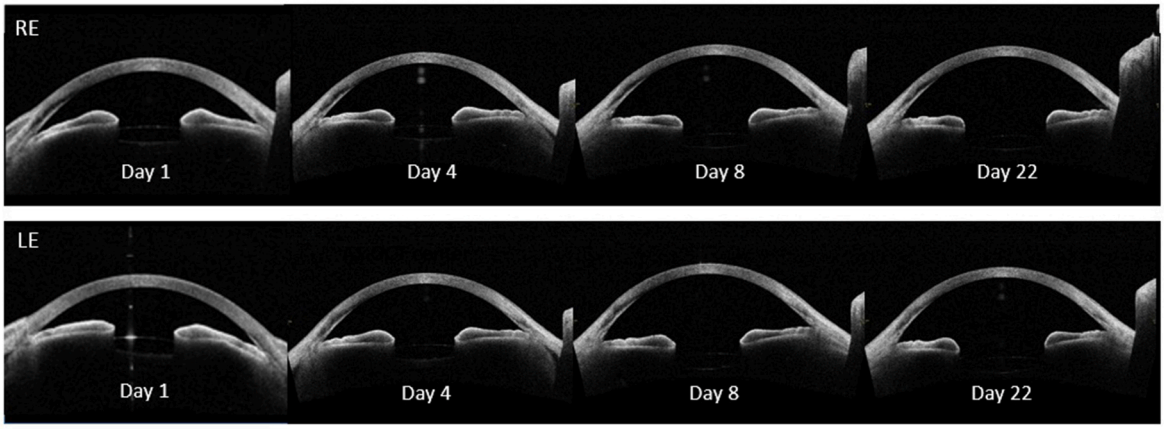

Fig. 3. Anterior segment optical coherence tomography shows a gradual increase of anterior chamber depth until stability on day 8.

compounds such as venlafaxine,[7] escitalopram,[8] isotretetoin,[9] zolmitriptan[10] and sumatriptan[11] have also been described in the literature.

Our case presented with acute bilateral angle closure with myopic shift. As the anterior segment imaging clearly demonstrated suprachoroidal fluid collection with anterior movement of the lens, it could be inferred that ciliochoroidal effusion was the mechanism of acute angle closure and myopia. Lee et al. and Edwards et al.[2,3] reported cases of secondary angle closure from daratumumab. Similar to ours, their cases showed bilateral IOP elevation with evident ciliochoroidal effusion. The onset of both cases was within 1 day, which was similar to ours. The condition gradually regressed with use of a cycloplegic agent and temporary anti-glaucoma medications. The choroidal effusions in our case and that of Lee et al. were resolved on days 14 and 16, respectively. In addition, Rasmussen et al. reported a case with choroidal effusion following daratumumab infusion, however, without angle closure and IOP change.[12] However, none of the cases was re-exposed to this monoclonal antibody.

Daratumumab is an IgG1k monoclonal antibody that binds to CD38 expressing cells. Studies have shown that daratumumab induces multiple myeloma cell death through several mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular

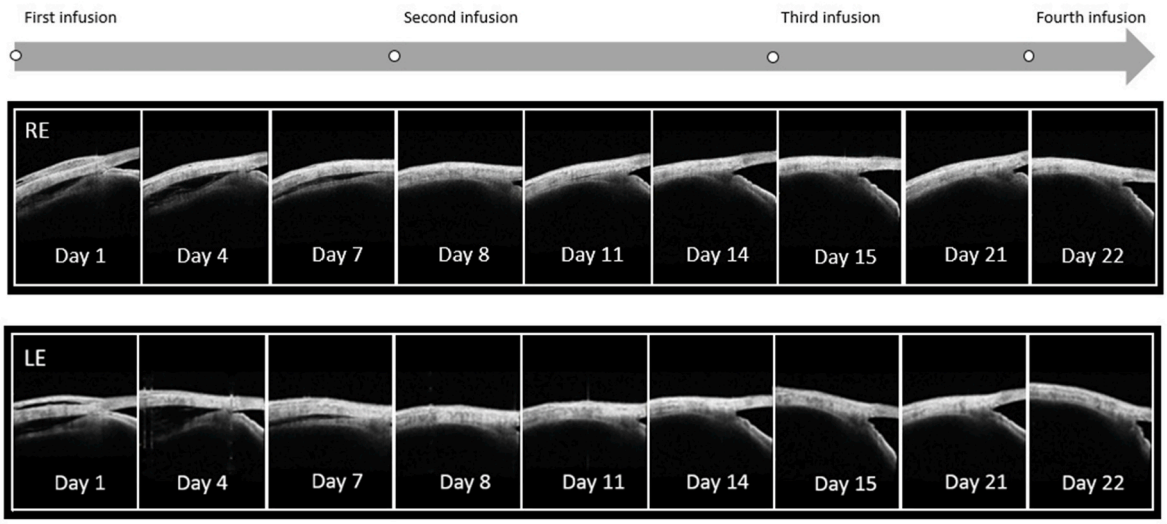

Fig. 4. Diagram shows a time sequence of daratumumab infusion and corresponding anterior segment optical coherence tomography. The ciliochoroidal effusion was apparent on day 1 and gradually decreased to complete resolution on day 14. No recurrence of the effusion was noted on day 8 (1 day after second infusion), day 15 (1 day after third infusion) or day 22 (1 day after fourth infusion).

phagocytosis (ADCP), and apoptosis.[13] IRRs occurs in approximately half of relapsed or refractory myeloma patients treated with daratumumab, with most occurring during the first infusion. Common mild daratumumab-related infusion reactions includes nasal congestion, throat irritation, coughing, chills and nausea and vomiting, while severe IRRs are characterized by dyspnea, laryngeal edema, bronchospasm, pulmonary edema, dyspnea, hypoxia and hypertension.[14] Studies in vertebrate eyes found CD38 expression in several locations in the retina including the Müller cell,[15] ganglion cell layer, inner nuclear layer and pigmented epithelium.[13] CD38 was also expressed in rat ciliary body in both the pigmented and non-pigmented epithelium.[13] In humans, CD38 was shown in corneal limbal epithelium.[16] The exact pathophysiology of how daratumumab causes ciliary effusion remains unclear. Regarding biomolecular explanation, we speculated that daratumumab may interact with CD38 glycoprotein on the ciliary body, which potentially leads to ciliary effusion.

To the best of our knowledge, daratumumab is the first known anticancer drug to induce angle closure. Unlike the situations involving other angle-closure-inducing medications in which other treatment options are available, certain cancer patients have limited alternatives. Our case was non-responsive to several other chemotherapy regimens, which necessitated re-exposure to daratumumab. Fortunately, there was no recurrence of either angle closure glaucoma or myopia after consecutive administrations of this drug.

There is limited information on the rechallenging test and existing studies show controversial results. Fraundelder et al. found three cases of topiramate-induced angle closure with a positive rechallenge test when medication was given at the same dosage.[17] However, another three reports found no recurrence after repeated drug administration.[18–20] We were unable to conclude whether the negative rechallenge in our case was due to a prophylactic effect of cycloplegic drug or whether this adverse reaction to daratumumab occurred in an idiosyncratic pattern. Although discontinuation of the offending agent is generally recommended following an episode of drug-induced angle closure, it may be acceptable to continue daratumumab if other treatment options are restricted. However, close monitoring is necessary.

Conclusions

Acute bilateral angle closure glaucoma can occur following daratumumab infusion. The awareness of oncologists and ophthalmologists of this potential ocular side effect can help in early recognition of the condition and minimalize visual damage. With the potential prophylactic effect of cycloplegic drug, it may be acceptable to continue daratumumab infusion under close monitoring.

Patient consent

The patient consented to publication of the case in writing.

Funding

No funding or grant support.

Authorship

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

Declaration of competing interest

The following authors have no financial disclosures: AS, WW, SC, AM, VT, NA.

Acknowledgements

None.

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