American Journal of Ophthalmology Case Reports 25 (2022) 101392

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Belantamab mafodotin associated corneal microcyst-like epithelial changes

Katherine Chuang [a], Roberto Pineda [b], Shaohui Liu [a,*]

[a] Eugene & Marilyn Glick Eye Institute, Indiana University School of Medicine, 1160 W. Michigan St., Indianapolis, IN, USA
[b] Massachusetts Eye and Ear Infirmary, Harvard Medical School, 243 Charles St., Boston, MA, 02114, USA

ARTICLE INFO

Keywords:
Belantamab mafodotin
Cornea
Drug adverse effects

ABSTRACT

Purpose: To report a case of bilateral corneal microcyst-like epithelial changes associated with belantamab mafodotin (belamaf) therapy.

Observations: A 70-year-old man with refractory multiple myeloma was placed on belamaf, a recently FDA-approved treatment for relapsed or refractory multiple myeloma. He developed decreased visual acuity and bilateral corneal microcyst-like peripheral epithelial changes. Belamaf was withheld.

Anterior segment OCT showed intra-epithelial opacities at various depths. After resolution of corneal changes and recovery of vision, belamaf was restarted. The patient underwent two additional treatments, each time with recurrence of diffuse microcyst-like corneal epithelial changes. It took a total of 8, 11.5 and 17 weeks after each respective infusion for the microcyst-like epithelial changes to resolve. This suggested a longer recovery time after each subsequent infusion.

Conclusions and importance: The care for patients on belamaf requires the collaboration of eye care providers and hematologists-oncologists to assess for ocular adverse effects and adjust treatment as necessary. Further study is needed to illustrate the mechanism of corneal microcyst-like epithelial changes and its effects on limbal stem cells.

1. Case report

A 70-year-old man with multiple myeloma that had relapsed despite multiple therapies was placed on belantamab mafodotin (belamaf), a recently approved FDA treatment for relapsed or refractory multiple myeloma. Thirteen days after belamaf infusion during a scheduled post-infusion visit, diffuse peripheral microcyst-like epithelial changes and mild punctate epithelial erosions were noted in the corneas of both eyes (Fig. 1A). The microcyst-like epithelial changes were present 360° in the peripheral cornea sparing the limbus. There was absence of fluorescein staining over most of the microcyst-like changes. Best corrected visual acuity with manifest refraction decreased from 20/25 to 20/40 bilaterally. Belamaf was withheld due to the ophthalmic findings. Three weeks later, the microcyst-like epithelial changes assumed a patchy appearance, migrating towards the center of the cornea (Fig. 1B). Anterior segment OCT (Cirrus HD-OCT 5000, Zeiss) showed intra-epithelial opacities at various depths (Fig. 1C). Resolution of corneal changes and recovery of vision occurred in another three weeks. The patient underwent two additional treatments with belamaf, each time with recurrence of diffuse microcyst-like epithelial changes within three weeks after infusion. Belamaf was held until the corneal epithelium improved to mild superficial keratopathy or better. It took a total of 8, 11.5, and 17 weeks after each respective infusion for the microcyst-like epithelial changes to resolve. There were whorl-like pigmentary changes in the corneal epithelium even 6.5 months after the third infusion. This suggested a longer recovery time after each subsequent infusion. The multiple myeloma responded robustly to belamaf, with continued and sustained decrease in free kappa light chains and M spike on serum protein electrophoresis despite delays in belamaf infusion. The patient developed significant cataract from chronic oral steroid use and underwent cataract surgery after the resolution of the microcyst-like epithelial changes from the third infusion. Uncorrected vision improved to 20/20 bilaterally after cataract surgery.

2. Discussion

Belantamab mafodotin is an antibody-drug conjugate that targets the B-cell maturation antigen on multiple myeloma cells, allowing for targeted delivery of a microtubule-disrupting agent named monomethyl auristatin F.[1] In the phase 2 clinical trial of the drug (Belantamab

* Corresponding author. Eugene & Marilyn Glick Eye Institute, Indiana University School of Medicine, 1160 W. Michigan St., Indianapolis, IN, 46202, USA.
E-mail address: liu486@iu.edu (S. Liu).

https://doi.org/10.1016/j.ajoc.2022.101392
Received 6 January 2021; Received in revised form 28 January 2022; Accepted 31 January 2022
Available online 2 February 2022

mafodotin for relapsed or refractory multiple myeloma or DREAMM-2 trial), 70% of subjects experienced keratopathy-related adverse events.[2] Corneal findings fall into 4 grades characterized by mild superficial keratopathy worse from baseline (Grade 1); moderate superficial keratopathy with or without patchy microcyst-like epithelial changes, peripheral sub-epithelial haze, or peripheral stromal opacity (Grade 2); severe superficial keratopathy with or without diffuse microcyst-like epithelial changes, central sub-epithelial haze, or central stromal opacity (Grade 3); and corneal epithelial defect such as an ulcer (Grade 4).[3] While still an active area of study, belamaf is thought to reach the cornea through the vascularized limbus or the tear film.[3] From there it is hypothesized that the drug is taken up by basal epithelial cells through macropinocytosis, which has been observed in *in vitro* studies of another antibody-drug complex AGS-16C3F.[4] It has been postulated that belamaf-containing cells can be seen as the microcyst-like changes that migrate centripetally to the center of the cornea and are extruded with routine replenishing of the corneal epithelium, though this is yet to be confirmed with histological studies.[3] Another antibody-drug conjugate, depatuxizumab mafodotin (ABT-414), granted orphan drug status for glioblastoma in 2014, had corneal findings similar to belamaf.[5]

Of note, it took a longer time for our patient to recover from the corneal epithelial changes after each subsequent infusion, echoing the delayed recovery seen after repeated belamaf administration in other series.[6] Bausell et al. found that over time, two thirds of patients receiving belamaf developed whorl-like keratopathy suggestive of limbal stem cell deficiency.[6] Further studies are required to reveal the impacts of belamaf on limbal stem cells.

Patients receiving belamaf should receive eye exams prior to initiating therapy and prior to each infusion to monitor for corneal toxicity.[3] If grade 2 or higher corneal findings are observed, consideration of holding the medication should be discussed with the patients' oncologists. The patients should be examined periodically until keratopathy improves to grade 1 or better, after which belamaf can be reinstated. Such dependence of the belamaf regimen on ophthalmic examination requires frequent communication between the eye care providers and hematologists to avoid delays in care. Aggressive management of dry eye is recommended to provide symptom relief. Topical steroid eye drops are not recommended as they were shown to be ineffective in preventing keratopathy.[2] Lastly, cold compresses over the eyes or limbal vasoconstriction with topical phenylephrine or brimonidine may be helpful at the time of belamaf infusion if the limbal vasculature is involved in the uptake of the drug.

3. Conclusions

The use of belamaf in the treatment of relapsed or refractory multiple myeloma has great potential for improving patients' quality of life but is not without adverse effects. The care for patients on belamaf requires the collaboration of eye care providers and hematologists-oncologists to assess for ocular adverse effects and adjust treatment as necessary. Further study is needed to illustrate the mechanism of corneal microcyst-like changes and its effects on limbal stem cells.

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.

Funding

Supported by a Challenge Grant from Research to Prevent Blindness, USA.

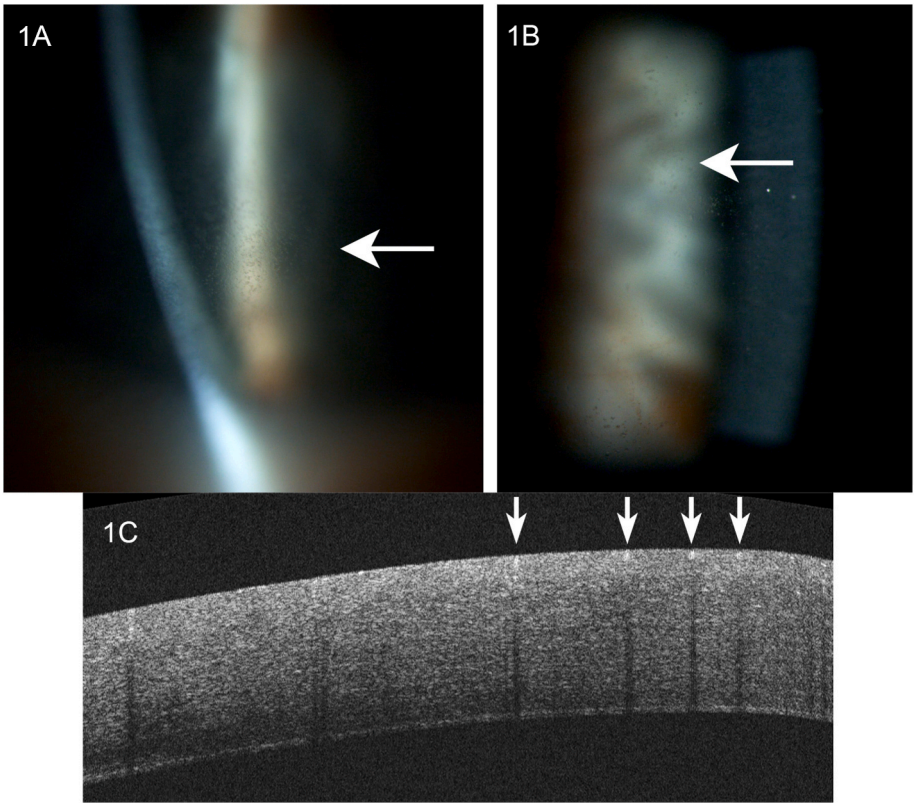

Fig. 1. Belamaf-associated epithelial keratopathy. Slit lamp photos showed initial peripheral microcyst-like epithelial changes (arrow, 1A), which later assumed a patchy appearance in the central cornea (arrow, 1B). Anterior segment OCT showed intra-epithelial opacities at various depths (arrows, 1C).

Authorship

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

Declaration of competing interest

The following authors have no financial disclosures: K·C., R.P. S.L. is an external consultant for GlaxoSmithKline LLC.

Acknowledgements

None.

References

1. Markham A. Belantamab mafodotin: first approval. *Drugs*. 2020;80(15):1607–1613.
2. Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol*. 2020;21(2):207–221.
3. Farooq AV, Degli Esposti S, Popat R, et al. Corneal epithelial findings in patients with multiple myeloma treated with antibody-drug conjugate belantamab mafodotin in the pivotal, randomized, DREAMM-2 study. *Ophthalmol Ther*. 2020;9(4):889–911.
4. Zhao H, Atkinson J, Gulesserian S, et al. Modulation of macropinocytosis-mediated internalization decreases ocular toxicity of antibody-drug conjugates. *Cancer Res*. 2018 Apr 15;78(8):2115–2126.
5. Lee BA, Lee MS, Maltry AC, et al. Clinical and histological characterization of toxic keratopathy from depatuxizumab mafodotin (ABT-414), an antibody-drug conjugate. *Cornea*. 2021 Sep 1;40(9):1197–1200.
6. Bausell RB, Soleimani A, Vinnett A, et al. Corneal changes after belantamab mafodotin in multiple myeloma patients. *Eye Contact Lens*. 2021;47(6):362–365.