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Intraepithelial corneal deposits associated with Mirvetuximab soravtansine use for platinum-resistant ovarian cancer

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ABSTRACT

Purpose: Present a case of Mirvetuximab soravtansine (MIRV)-induced intraepithelial corneal deposits, review a proposed mechanism to explain the blurred vision our patient experienced, and explain clinical exams that may be used to support the diagnosis.

Observations: A 63-year-old female with metastatic ovarian cancer diagnosed with intraepithelial corneal deposits two weeks after her first MIRV infusion. Treatment with topical prednisolone acetate 1 % ophthalmic suspension and lubricating eye drops without interruption of her MIRV infusions resulted in complete resolution of blurry vision and corneal deposits.

Conclusions and importance: The natural reversibility of MIRV-induced keratopathies underscores the need for prompt and regular ophthalmic assessments throughout drug administration. Understanding the mechanism behind these corneal changes, how to recognize them in a clinical setting, and expedite their reversal are essential to improve quality-of-life metrics in patients receiving MIRV transfusions.

1. Introduction

Mirvetuximab soravtansine (MIRV), also known as Elahere, is an antibody-drug conjugate that was FDA approved for treatment of folate receptor alpha (FRα) platinum-resistant ovarian cancer in November 2022.[1] It comprises of an antibody that targets the FRα protein on cell surfaces, a cleavable linker, and a potent cytotoxic agent called DM4. When MIRV binds to FRα, the complex is internalized and DM4 is released to suppress microtubule dynamics, leading to cell cycle arrest and cell death.[2,3] The design of MIRV's cleavable linker allows active DM4 to diffuse from the targeted tumor cells to nearby cells, triggering apoptosis independently of the target, a phenomenon known as 'bystander' killing.[2,4,5] In the SORAYA (NCT04296890) and FORWARD I (NCT02631876) clinical trials, the most frequently reported treatment-related adverse events were blurred vision (43 % and 42 %, respectively), keratopathy (31 % and 32.5 %, respectively), and nausea (31 % and 45.7 %, respectively).[4,5] In these clinical trials, the term "keratopathy" was used broadly to encompass various specific conditions, including corneal cyst, corneal disorder, corneal epithelial microcysts, keratitis, limbal stem-cell deficiency, corneal opacity, corneal erosion, corneal pigmentation, corneal deposits, interstitial keratitis, punctate keratitis, and corneal epithelial defect. Here, we present intraepithelial corneal deposits as an ocular adverse effect associated with Mirvetuximab soravtansine use, describe its clinical features, and offer a proposed mechanism to explain the blurred vision that MIRV can cause.

2. Case report

A 63-year-old female with a medical history notable for current metastatic ovarian cancer presented to the ophthalmology clinic complaining of blurry vision that was worse in the right eye without irritation or pain. At the time of presentation, the patient had undergone one standard Elahare infusion for her ovarian cancer, specifically a 6mg/kg dose on a three-week cycle. The patient reported that her symptoms of blurry vision began three days after her first MIRV infusion. Importantly, she did not receive an ophthalmic exam nor was she prescribed ophthalmic topical steroids prior to MIRV initiation. She reported to the ophthalmology clinic two weeks after her first MIRV infusion. On exam, right eye corrected distance visual acuity (VA) was measured to be 20/70–1 with a pinhole VA of 20/30–1, while the left eye corrected distance VA was 20/50 and pinhole VA was 20/25. Corneal deposits were

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visualized in the anterior corneal stroma of both eyes through slit lamp examination (Fig. 1). Rotating scheimpflug tomography (Pentacam, Oculus) demonstrated anterior stromal and subepithelial opacities inferiorly in the right cornea and centrally in the left cornea, associated with localized corneal steepening (Fig. 2A). Otherwise, the ophthalmic exam was unremarkable.

Per Elahare protocol, topical Prednisolone Acetate 1 % ophthalmic suspension was prescribed and initiated following this first ophthalmology visit. Instructions were to administer these drops six times daily in both eyes beginning the day before her Elahare infusion for six days, followed by four times daily for four days. The patient was also prescribed preservative free lubricating eye drops three times daily. She continued to receive Elahare infusions on a three-week cycle as prescribed by her oncologist to treat her metastatic ovarian cancer, without abating.

After six weeks, the patient reported improved visual acuity in her previously blurry right eye. On follow up exam, the patient's corrected distance visual acuity measured 20/25–2 in both eyes with no change on pinhole examination for either eye. On slit lamp examination, anterior corneal deposits were present but reduced compared to the original examination. Pentacam findings displayed improved shape bilaterally (Fig. 2B). After six more weeks, the patient reported complete resolution of blurry vision. Her corrected distance visual acuity measured 20/20 in both eyes with no change on pinhole examination. No corneal deposits were seen by slit lamp examination, and Pentacam photos showed significantly improved corneal shape bilaterally (Fig. 2C).

3. Discussion

The use of antibody-drug conjugate MIRV is gaining popularity with its recent FDA approval for the treatment of FRα platinum-resistant ovarian cancer. As mentioned previously, MIRV consists of an FRα-directed antibody, a cleavable linker, and a potent cytotoxic agent called DM4 which inhibits microtubule dynamics, leading to apoptosis.[4] Several ocular adverse effects, specifically corneal conditions, are associated with MIRV. Various articles have highlighted MIRV's potential for such treatment-related ocular effects, and a few have focused exclusively on these unfavorable ocular reactions.[4,6–11]

It is unlikely that the MIRV antibody induces corneal toxicity via antibody targeting given the FRα-free environment of the cornea.[8,9] Rather, current literature explains that the DM4 cytotoxic payload is the probable culprit, hindering mitosis in the cornea's epithelial layer.[5,7–9] Some postulate that the cleavable linker may extend MIRV's half-life, potentially contributing to increased ocular epithelial exposure to MIRV.[5,8] Coribelli et al. offer a case series regarding the development of fine corneal subepithelial opacities in five patients, all of which experienced reversibility of opacities, similar to our patient's case. The article also ponders the potential pathogenesis of MIRV-induced corneal pathology mentioning the eye's strong blood supply, highly proliferative cells, and plethora of cell receptors. However, there is no proposed mechanism for the blurred vision that these patients experience in the report.

The pinhole test is a commonly used assessment to distinguish whether reduced visual acuity is caused by refractive errors or ocular disease, such as cataracts or macular degeneration. For this test, an opaque disc with a 1.2mm hole is placed over the patient's eye to focus light, temporarily mitigating the effects of refractive errors. If a patient's visual acuity improves with the pinhole device, it may indicate the presence of an uncorrected refractive error. On initial examination, our patient presented with extensive bilateral anterior corneal opacities and bilateral corneal steepening. The pinhole test revealed improved visual acuity, suggesting the presence of a potential refractive error likely caused by an altered corneal shape. When our patient returned six weeks later with reduced corneal deposits, improved corneal shape, and improved visual acuity, her pinhole test was unremarkable. Although we did not perform a formal refraction test at each visit, and we cannot definitively say that the patient's refraction changed, the pinhole test findings reinforce the anticipated relationship between MIRV-induced corneal deposits, corneal curvature, and the hinted refractive error potentially causing our patient's blurred vision. A case series by Canestraro et al. discusses refractive shifts, central epithelial hyperplasia, and corneal shape changes congruent with our case findings in patients with antibody-drug conjugate-induced keratopathy.[7]

A few articles offer a possible mechanism behind changes in corneal topography due to MIRV-induced corneal epithelial deposits, otherwise called microcyst-like epithelial changes (MECs)[5,8] On examination of patients taking MIRV, MECs are initially located peripherally and migrate centrally, supported by the variable locations of corneal subepithelial opacities, including central stromal arrangement, in our patient.[5,8] Importantly, while the cornea is a non-vascularized tissue, the limbus contains blood vessels which serve as a highway for MIRV molecules from the bloodstream to reach both the limbus and the neighboring cornea. Epithelial progenitor cells from the limbus move centripetally to maintain and regenerate the corneal epithelium.[12] MIRV molecules follow these cells' migration, leaving a trail of corneal epithelial apoptosis and MECs that ultimately alter the cornea's terrain.[5,7,8] The natural capacity of the limbus to restore corneal cells that have undergone apoptosis may explain the transient nature of MIRV-induced corneal pathology.[8] Due to the significant number of ocular adverse effects associated with MIRV treatment, patients receiving MIRV infusions are recommended to undergo a full ophthalmic examination prior to the initiation of therapy, at the end of

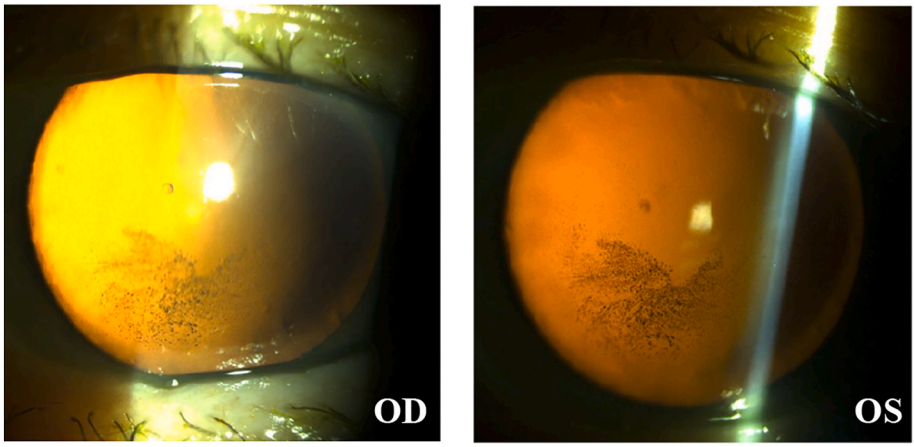

Fig. 1. Right (OD) and left (OS) corneas viewed by retro-illumination slit lamp technique showing corneal deposits in the anterior corneal stroma of both eyes at the first visit.

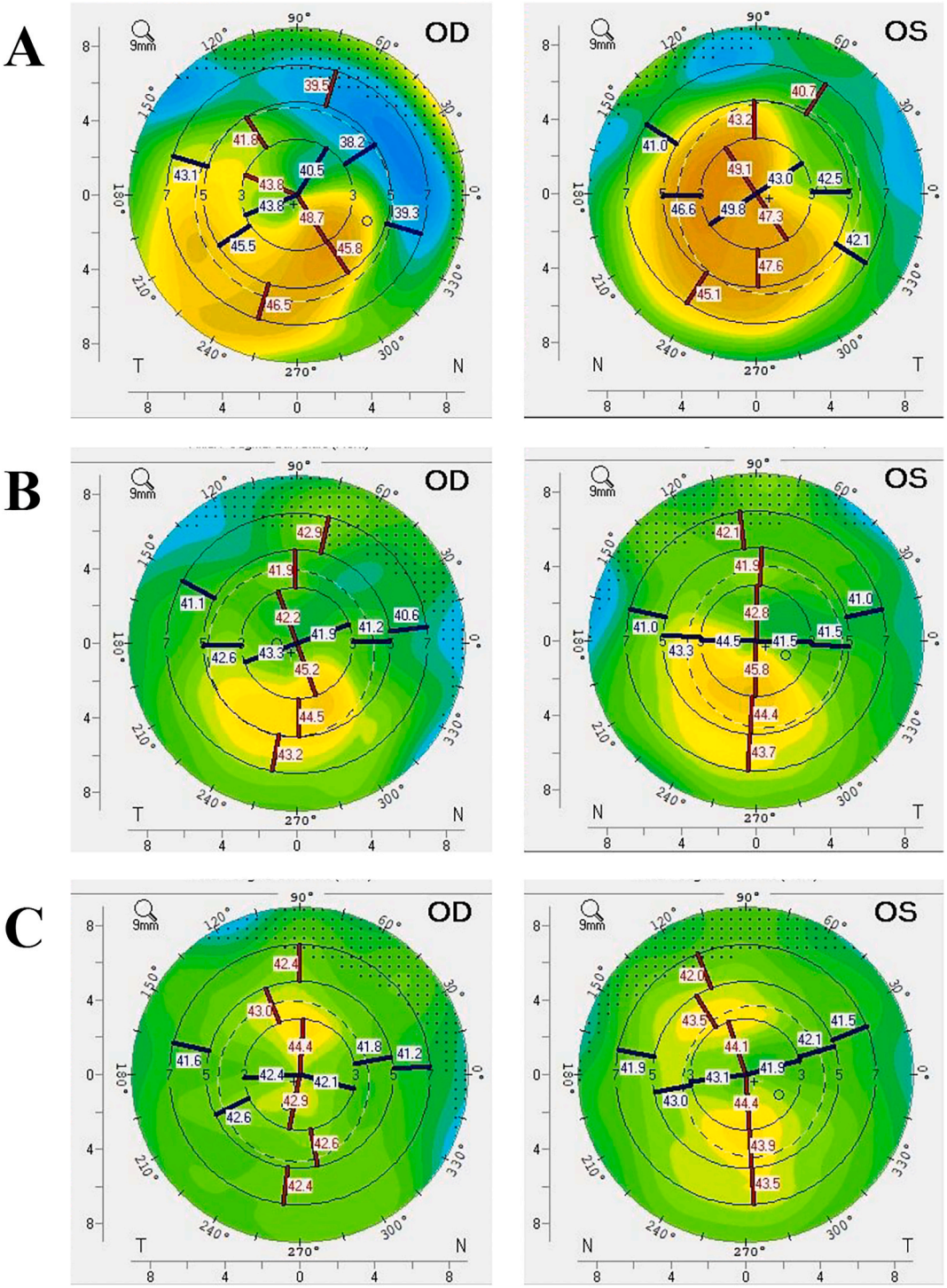

Fig. 2. (A) Right (OD) and left (OS) corneal axial curvature maps from the Pentacam at the first visit, anterior stromal and subepithelial opacities inferiorly in the right cornea and centrally in the left cornea associated with localized corneal steepening. (B) Right (OD) and left (OS) corneal axial curvature maps from the Pentacam at the second visit, improved corneal steepening bilaterally. (C) Right (OD) and left (OS) corneal axial curvature maps from the Pentacam at the third visit, significantly improved corneal shape bilaterally.

every other cycle, and as clinically indicated.[8] It is also wise for these patients to use corticosteroid drops and lubricating drops daily to avoid MIRV-related ocular adverse effects and vision changes.[9,13] As inflammation is not a proven attribute of MIRV keratopathy,[5,8] steroids are an effective treatment for alternative mechanisms than inhibiting inflammation. Steroids may promote desquamation of the corneal epithelium, precipitating corneal regeneration and reversal of pathology.[5,8]

The SORAYA clinical trial specifically classifies MIRV-induced ocular adverse effects using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0).[5,8,10,14] CTCAE grade 3 is defined as symptomatic ocular effects, with prominent decrease in visual acuity worse than 20/40.[10] Our patient's initial left eye corrected distance VA of 20/50 classifies her as a grade 3 upon presentation. For CTCAE grade 3 ocular symptoms, the FDA's MIRV Prescribing Information currently advises withholding MIRV until a CTCAE of grade 1 (or baseline) or less is achieved, then resume at one lower dose level.[14] In

the SORAYA trial, MIRV treatment was abated upon a milder CTCAE grade of 2 or more, including blurry vision or irritation, and only resumed once ocular symptoms resolved to grade 1 (or baseline) within four weeks of the next MIRV dose.[8] Our patient remarkably improved from CTCAE grade 3 to grade 1, with complete reversal of keratopathy by prednisolone and lubricating eye drops, all while continuing the patient's MIRV at its original dose. Exceptionally, our patient's potentially life-saving treatment was not sacrificed to ameliorate her onerous ocular symptoms.

4. Conclusion

The natural reversibility of the MECs seen in our patient underscores the need for prompt and regular ophthalmic assessments throughout MIRV administration. MIRV-induced keratopathies can ultimately reduce a patient's quality of life, yet the current literature lacks ample explanations for these ocular adverse effects. Understanding the mechanism behind these corneal changes, how to recognize them in a clinical setting, and expedite their reversal are essential to mitigate symptoms that affect quality of life in patients receiving MIRV transfusions.

CRediT authorship contribution statement

Charlotte McRae: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. **Rachael Cowan:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Macy Green:** Writing – review & editing, Visualization, Validation, Resources, Investigation, Data curation, Conceptualization. **Jack S. Parker:** Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Patient consent

The patient consented to the publication of the case in writing.

Authorship

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

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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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