Case Report

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Corneal epithelial changes in a patient treated with belantamab mafodotin

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Abstract:

The aim of the study is to report a case of corneal epithelial changes in a patient with refractory multiple myeloma (MM) who was treated with belantamab mafodotin (BM). A 55-year-old man diagnosed with refractory MM was referred to our hospital for treatment with BM, an antibody-drug conjugate targeting B-cell maturation antigen. After 33 days of treatment, the patient experienced a bilateral reduction in visual acuity (VA), along with dry eye symptoms such as itchy eyes and a sensation of having a foreign body. Slit-lamp examination revealed the presence of diffuse microcystic epithelial changes throughout the cornea. BM treatment was discontinued by the oncologist. Sixty days after stopping belantamab, VA gradually improved and the microcystic epithelial alterations progressively diminished. Ninety days after discontinuation of therapy, only a few microcystic epithelial alterations remained, and the patient had 20/20 VA in both eyes. While BM is an effective therapy for refractory MM, corneal epithelial changes are among the most common side effects of this treatment. Close collaboration between ophthalmologists and oncologists is crucial for assessing ocular adverse effects and tailoring treatment accordingly.

Keywords:

Adverse effects, belantamab, epithelial changes, mafodotin, relapsed or refractory multiple myeloma

Introduction

Multiple myeloma (MM) is a rare hematopoietic malignancy, accounting for 1%–2% of all malignancies and is characterized by uncontrolled proliferation of plasma cells.[1,2] It typically affects people in their third decade of life.[2,3] The therapeutic approach for MM includes immunomodulatory agents, proteasome inhibitors, and anti-CD38 monoclonal antibodies.[4-6] However, in cases of subsequent relapses or refractory MM (RRMM), treatment becomes more challenging with a poor prognosis.[7,8]

In recent years, new therapeutic approaches have emerged; among them, belantamab mafodotin (BM) appears to be the most promising. BM is an antibody-drug conjugate (ADC) composed of a monoclonal antibody targeting B-cell maturation antigen conjugated to the microtubule inhibitor monomethyl auristatin F (MMAF). It was Food and Drug Administration approved the treatment of RRMM in 2020.[9]

Two studies (DREAMM-1 and DREAMM-2) have demonstrated the activity of BM in RRMM patients.[8,10,11] Notably, the DREAMM-2 study reported that up to 74% of the patients developed ocular surface adverse events, particularly superficial keratopathy with microcystic-like epithelial changes (MECs) in the corneal epithelium.[11] Blurred vision and dry eye symptoms were the most commonly reported symptoms associated with MECs.

MECs spontaneously resolved in 54% to 73% of patients several months after treatment and could be observed using slit-lamp microscopy, anterior segment optical coherence tomography (AS-OCT), or laser scanning *in vivo* confocal microscopy (IVCM).[11,12] The authors proposed a "keratopathy and visual

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acuity" (KVA) scale to evaluate belantamab-associated superficial keratopathy (BASK), based on the severity of keratopathy and visual loss. KVA is divided into four grades ranging from mild to severe, with Grade 1 showing mild keratopathy and declines in best-corrected visual acuity (BCVA) up to 1 line, and Grade 4 characterized by corneal epithelial defects and/or corneal ulcers with BCVA worse than 20/200.[12,13] Although the adverse effect may necessitate temporary cessation or discontinuation of treatment, therapy can generally be restarted after the resolution of epithelial defects.[14]

In this report, we describe a case of a 55-year-old man with RRMM treated with BM who developed bilateral BASK.

Case Report

A 55-year-old man presented to our clinic for a comprehensive eye examination before initiating therapy with BM for RRMM. The patient had a history of radial keratotomy for myopia in 1992 and photorefractive keratectomy (PRK) in 2000 for myopic shift. He reported an allergy to topical fluorescein, which prevented us from performing a slit-lamp examination with blue cobalt light and a break-up time test.

During the initial visit, no ocular abnormalities were noted. VA was 20/20 in both eyes, and intraocular pressure (IOP) was 11 mmHg in the right eye (RE) and 13 mmHg in the left eye (LE). The ocular surface disease index (OSDI) was 7, and Schirmer's test was normal with a value >10 mm in both eyes. Slit-lamp examination revealed the presence of ten radial keratotomies and subepithelial ferrous deposits, likely due to the PRK treatment. Corneal central thickness (CCT), measured by ultrasound pachymetry, was 565 µm in the RE and 569 µm in the LE. The fundus examination was normal in both eyes. The patient initiated BM infusion (2.5 mg/kg) the day after the ophthalmological evaluation (day 0), and the second infusion was administered on day 21.

After 33 days of treatment, the patient returned for a scheduled visit complaining of blurred vision and dry eye symptoms. A reduction in VA was noted, with VA of 20/50 in the RE and 20/100 in the LE. OSDI score was 15, and Schirmer's test was >10 mm in both eyes. Slit-lamp examination revealed subepithelial microcystic changes consistent with MECs and superficial diffuse epithelial keratopathy [Figure 1]. CCT was 586 µm in the RE and 589 µm in the LE. The KVA grading system assigned a Grade of 2. IOP was 12 mmHg in the RE and 11 mmHg in the LE, and no fundus abnormalities were reported. Tear substitutes were prescribed to alleviate symptoms and mitigate drug toxicity. The patient was referred to a hematologist, and BM treatment was discontinued.

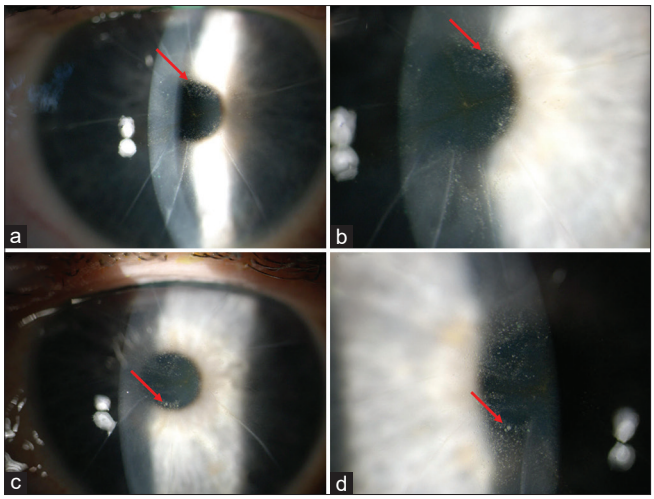

Figure 1: After 33 days of treatment with BM slit-lamp examination highlighted the presence of 10 radial keratotomies, central subepithelial ferrous deposits, and diffuse MECs (red arrow), (a and b) right eye, (c and d) left eye. BM: Belantamab mafodotin

After 30 days of BM discontinuation, the patient returned with the same symptoms. Ophthalmological assessments revealed no significant changes compared to the previous visit [Figure 2]. OSDI score was 14, and Schirmer's test was >10 mm in both eyes. CCT was 578 µm in the RE and 581 µm in the LE. IOP was 12 mmHg in both eyes. The patient's topical therapy with tear substitutes was continued.

The patient reported an improvement in VA and relief of dry eye symptoms 60 days after discontinuing BM. VA was 20/25 in the RE and 20/22 in the LE. OSDI score was 9, and Schirmer's test showed no change. Slit-lamp examination revealed a significant reduction in peripheral MECs and mild superficial epithelial keratopathy, graded as 1 on the KVA scale [Figure 3]. CCT was 568 µm in the RE and 572 µm in the LE. IOP was 13 mmHg in the RE and 12 mmHg in the LE.

Ninety days after BM interruption, the VA was 20/20 in both eyes, with only a few MECs, detected at SL examination in the central cornea. OSDI was 7, and Schirmer test was >10 mm in both eyes. CCT was 564 µm in the RE and 568 µm in the LE. Ocular pressure was 13 mmHg in both eyes.

With the improvement of the eye conditions, the hematologist proposed retreatment with BM, but the patient refused to continue because of previous adverse effects.

Discussion

BM has been shown to be a viable therapeutic option in patients with RRMM in the DREAMM-1 and DREAMM-2 trials.[10,15] It is an ADC that binds to a specific tumor cell surface antigen and induces apoptosis.[16] However,

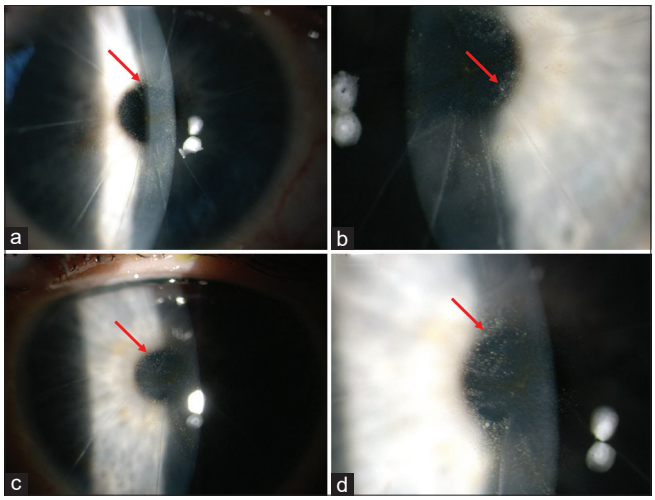

Figure 2: After 30 days from BM suspension, slit-lamp examination highlighted the persistence of MECs (red arrow), (a and b) right eye, (c and d) left eye. BM: Belantamab mafodotin

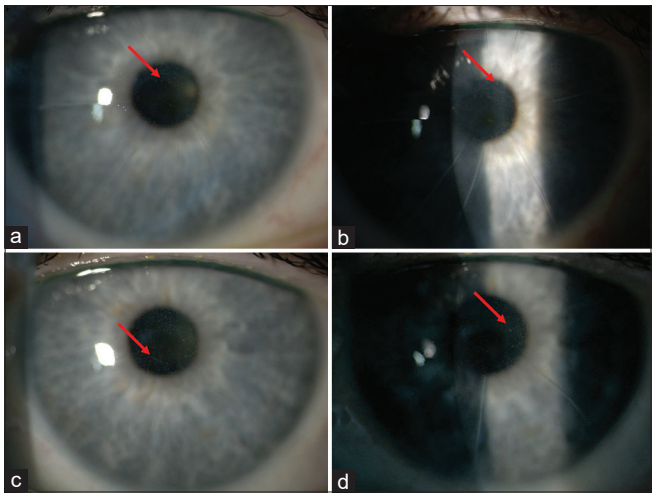

Figure 3: Slit-lamp examination in both eyes showed a reduction of MECs (red arrow) in the corneal periphery, (a and b) right eye, (c and d) Left eye

along with its beneficial effects, BM can also cause several ocular side effects, with the most common being superficial punctate keratopathy and/or the presence of MECs. Patients often report dry eye symptoms and blurred vision. Corneal changes can be observed with slit-lamp examination. However, AS-OCT and IVCM can also provide valuable support for follow-up.[17,18] These changes typically start in the peripheral cornea and then migrate toward the center, affecting vision quality and quantity.

Although the exact mechanism of ocular toxicity is unknown, several studies have shown a correlation with drug components such as microtubule-disrupting MMAF, which is a cytotoxic component of several ADCs that can cause ocular adverse effects through both on-target and off-target processes.[14,15,19,20] BM induces apoptosis in myeloma cells but may also induce apoptosis in corneal epithelial cells due to MMAF. The mechanism by which the drug reaches the cornea is unclear, but it may occur through tears or limbal vessels.[11] Based on the KVA scale, BM treatment can be reduced or suspended. The management of BM-related ocular toxicity depends on the severity of corneal alterations as determined by the KVA scale: for Grade 1, treatment can be continued and for Grades 2, 3, and 4, treatment should be postponed until the condition improves to a grade ≤ 1.[14,15] In this report, we describe a case of corneal alteration in a patient treated with BM for RRMM. MECs were observed 33 days after starting therapy, which is consistent with findings in the literature.[17] The patient was diagnosed with Grade 2 ocular toxicity on the KVA scale, and the hematologist decided to discontinue BM treatment.[15] Although the exact mechanism is unknown, several authors speculate that BM products may be internalized or deposited in corneal epithelial cells.[21] MECs were present throughout the cornea at the first follow-up visit, although previous studies have reported that MECs typically involve the peripheral cornea first and then progress towards the center.[15,17] Corneal changes in our patient likely started a few days before the visit and without any symptoms. According to the literature, significant reductions in MECs occur between 42 and 63 days after discontinuing the drug.[17] In our patient, MECs in the peripheral cornea were reduced 60 days after drug discontinuation. The activity of limbal stem cells, which replace corneal epithelial cells first in the periphery and then in the center, may be responsible for the resolution of corneal alterations. However, our patient did not show wave-like epitheliopathy or pannus, indicating that the exact etiopathogenesis of corneal alterations associated with BM is not completely understood. The DREAMM-2 trial reported that blurred vision and dry eye sensation are the most common symptoms in patients treated with a dose of 2.5 mg/kg of BM, which is consistent with our patient's complaints after 33 days of treatment.[11] Therefore, all patients receiving BM treatment require regular eye examinations before each infusion and throughout the treatment to monitor for corneal toxicity.

Although BM is a viable option for the treatment of RRMM patients, a close collaboration between ophthalmologists and hematologists is required for its management because of the drug's ocular side effects. However, the real-life incidence of these side effects is still unknown because few studies are available in the literature. Moreover, further studies are necessary to better understand how BM reaches the cornea. This is fundamental for preventing and treating ocular events and understanding the timing of intervention for drug suspension.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Data availability statement

The data that support the findings of this study are available from University Of Trieste but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of University of Trieste.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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