Théa inteRnational cOntest of clinical cases in PatHologies of the eYe (2024-2025)

When Skin Conditions Impact Ocular Surface Health

Conquering challenges in therapy-resistant mucocutaneous HSV-1 infection with severe herpetic keratitis and ocular Graft-versus-Host-Disease

Introduction

Herpes simplex viruses type 1 and 2 (HSV-1 and HSV-2) present at a high seroprevalence worldwide. (1, 2) Most ocular infections are caused by HSV-1, which is a highly effective neurotropic virus that predominantly targets the epithelial cells of the orofacial mucosa. (3) Following its initial lytic replication in the epithelial cells of the oral, ocular and nasal mucosa, HSV-1 enters a lifelong latent state in neurons located within the trigeminal ganglion. Thus, the virus is never completely eradicated, which can lead to reactivation. Recurrence can cause a range of illnesses in immunocompetent and immunosuppressed patients of all ages including mucocutaneous infections and regarding the eye a herpetic keratitis, which can lead to blindness in severe cases. (4) In immunocompromised patients, severe systemic infections can lead to rapid disease progression and considerable mortality. (5)

This case report presents a unique occurrence of a therapy-resistant mucocutaneous HSV-1 infection with severe keratitis complicated by ocular Graft-versus-Host-Disease (oGVHD) in an immunocompromised patient after allogeneic hematopoietic stem cell transplantation (aHSCT). Besides already established systemic antiviral therapy, the patient developed a severe mucocutaneous involvement and rapidly progressive geographic herpetic ulceration of the right eye. As the ocular condition could not be controlled under intensified topical therapy, a complete abrasion of the epithelium with subsequent amniotic membrane transplantation was performed. To complicate matters, the patient developed chronic oGVHD and microcyst-like epithelial changes afterwards. Due to proven treatment resistance, multiple antiviral medications including transfer of personalized antiviral allogeneic T-lymphocytes were established.

Case presentation

A 38-year-old woman underwent aHSCT due to acute myeloid leucemia in January 2023. Ophthalmological consultations before and after first aHSCT showed no signs of any ocular surface disease or oGVHD. At the first control after transplant the best spectacle-corrected visual acuity (BSCVA) was 0.1 log MAR on the right and 0 log MAR on the left eye. Intraocular pressure (IOP) was 8 mmHg on right and 9 mmHg on left eye. Esthesiometry was normal in both eyes. There was no corneal or conjunctival fluorescein staining. Ocular surface disease index (OSDI®) was 8.

As the patient suffered an early relapse of AML after aHSCT, a second aHSCT was performed in January 2024. One month after transplantation HSV-1 viremia and herpetic oral mucositis were detected via swab and PCR. Clinically, HSV-1 reactivation manifested itself at first with increasingly painful and severe oral and vulvar mucositis, which were extensively encrusted

and accompanied by bleeding. Antiviral therapy was immediately intensified with intravenous acyclovir adjusted to renal function. Seven days later the patient described ocular discomfort, redness and decreased visual acuity of her right eye. OSDI® was 50. Ophthalmological examination revealed confluent dendritiform epithelial lesions of the affected right eye and corneal fluorescein staining of the left eye. (Fig. 1)

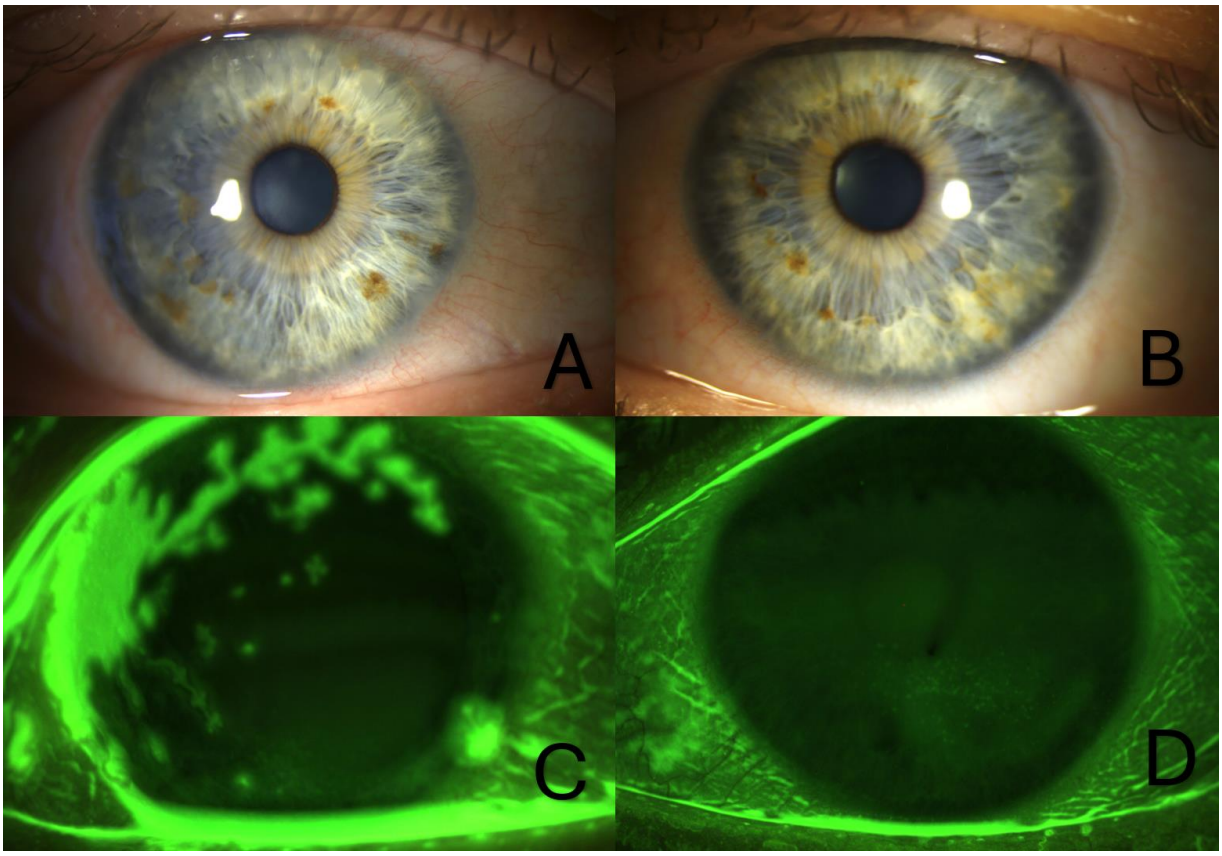

Figure 1 A shows the right eye and B the left eye during slit lamp examination. C and D show fluorescein staining of the right and left eye.

BSCVA was decreased to 0.3 log MAR in right and left eye. IOP was 20mmHg and 17 mmHg in right and left eye. Esthesiometry with Cochet-Bonnet revealed reduced sensitivity of the right eye (3/6cm). There was no intraocular involvement in the anterior or posterior segment of either eye. A corneal scrap for viral PCR of the right eye was performed and ganciclovir ointment was prescribed five times a day and ofloxacin eyedrops two times a day for the right and ganciclovir ointment two times a day for the left eye. Although topical and systemic therapy were quickly intensified, the patient developed rapid progression of every involved tissue. Figure 2 shows the dynamic changes of the epithelial defects of the right eye over a course of 3 weeks. BSCVA of the right eye was reduced to 0.7 log MAR. The left eye showed no signs of HSV-1 associated

keratitis. At this time, the scrap result of the right eye was received, which clearly detected HSV-1. An oral swab also confirmed the suspected acyclovir resistance, so systemic therapy was adjusted and foscarnet was initiated. Due to the persistent severe findings of the ocular surface (Fig. 2) without significant improvement under intensified topical therapy, an epithelial debridement with subsequent amniotic membrane transplantation was performed on the right eye. (Fig. 3) Fortunately, epithelial closure without evidence of recurrent herpetic keratitis was seen after only 2 weeks. BSCVA of the right eye improved to 0.4 log MAR. OSDI® improved to 25.

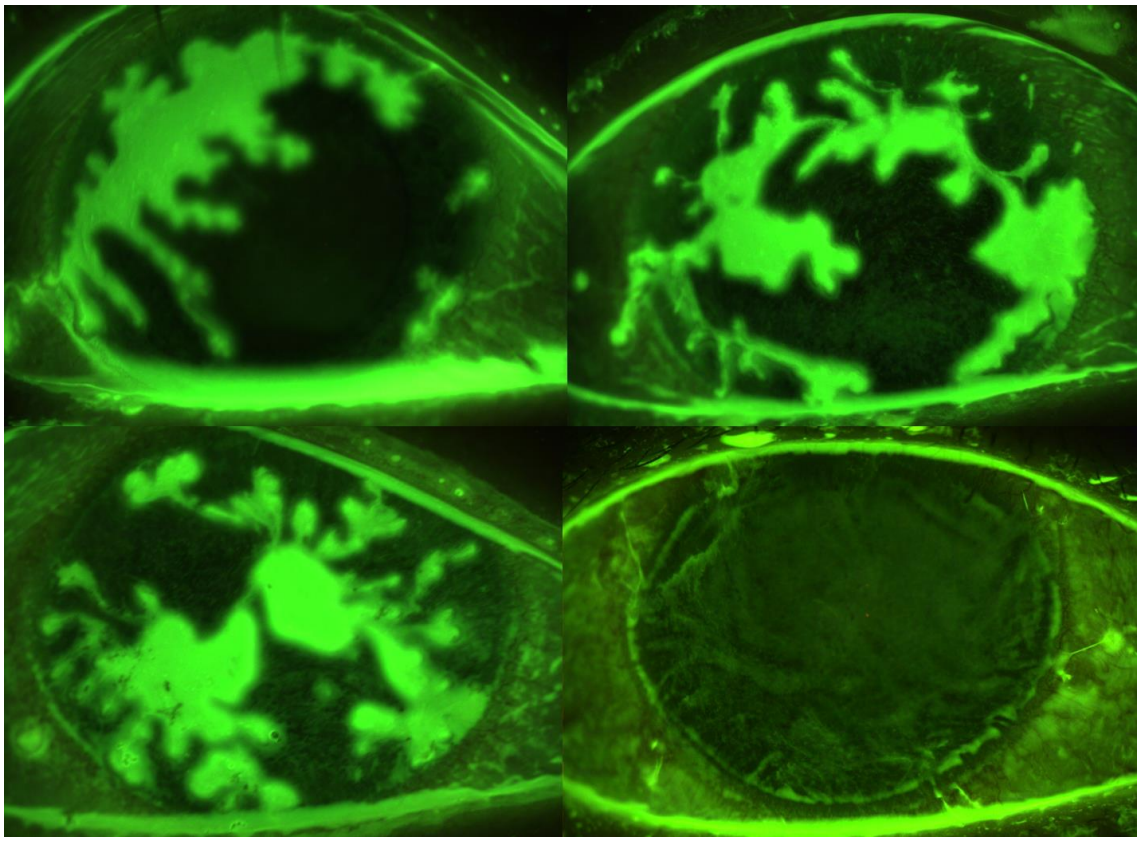

Figure 2 Both upper and the lower left pictures show the dynamic of the geographic ulceration. The picture in the right lower corner shows the fluorescein staining right after removal of the contact lens and conjunctival sutures after amniotic membrane was resolved.

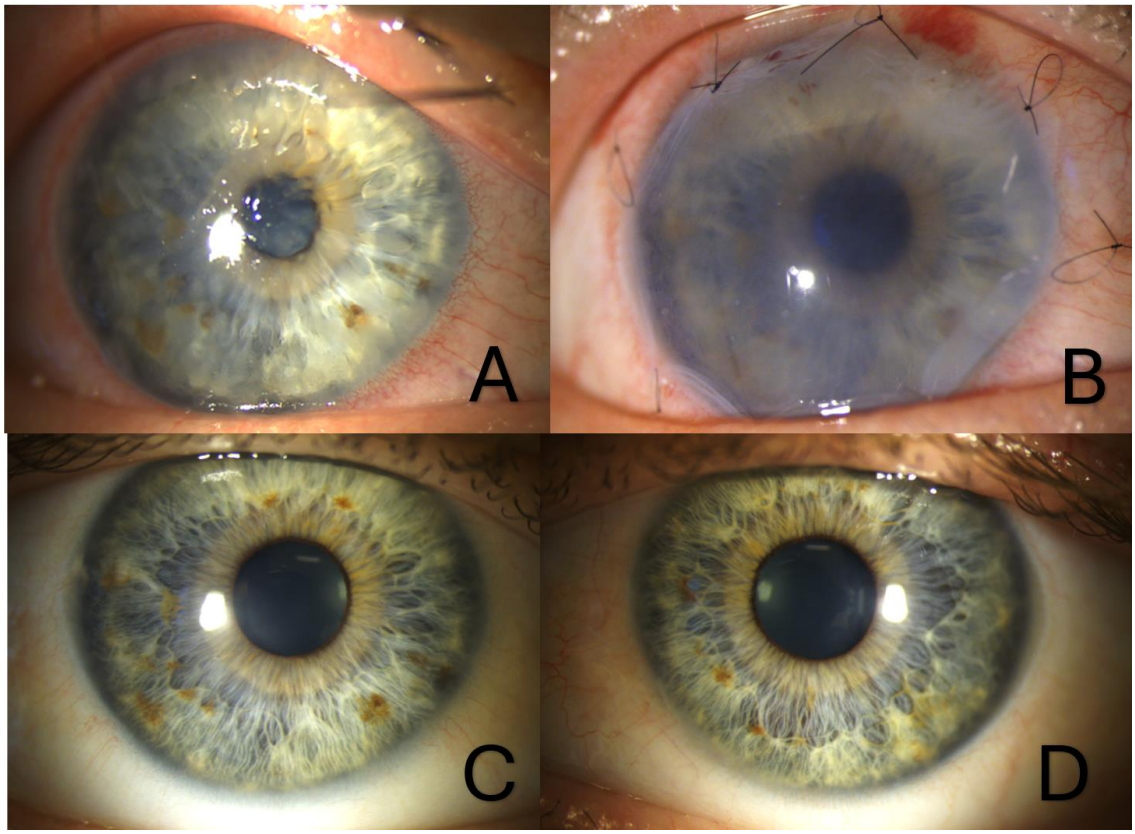

Figure 3 A shows the right eye before AMT. B shows the right eye with AMT and contact lens. C shows the right eye one week after removal of contact lens and resorption of AMT. D shows the left eye at the same time as C was taken.

However, within short time chronic GVHD of the skin developed and chronic oGVHD (NIH grade III) also emerged. Therefore, local therapy was supplemented with dexamethasone and ciclosporin eye drops. Systemic therapy targeting skin GVHD was established by the dermatologists and oncologists. Regarding systemic GVHD, treatment was especially challenging as further immunosuppression increases the risk of infectious diseases on one hand and could limit the desired graft-versus-leukaemia effect. Unfortunately, the established systemic antiviral therapy could not control viremia successfully and there was no significant clinical improvement in this regard. Additionally, both eyes started to develop significant microcyst-like epithelial changes (MECs) of both eyes with a corresponding loss of visual acuity to 0.6 and 0.4 log MAR. (Fig. 4)

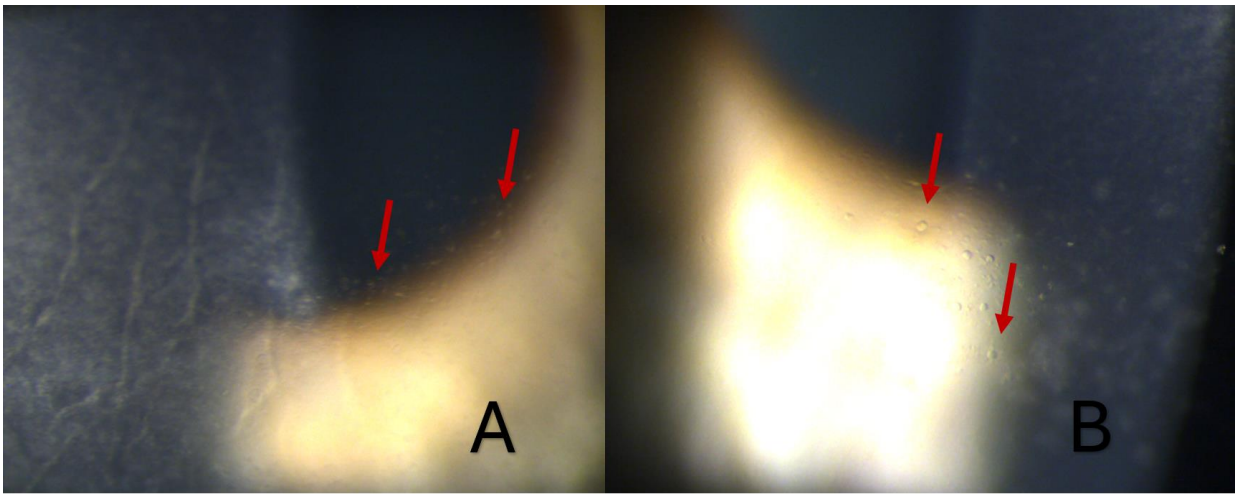

Figure 4 MECs and epithelial changes of the right (A) and left (B) eye. Red arrows point towards MECs as an example.

As a further extension of therapy, the antiviral therapy was switched to the experimental drug pritelivir and after 7 weeks to cidofovir. This was supported by a total of three infusions of personalized antiviral allogeneic T-lymphocytes. As we know, antiviral agents are often associated with a substantial renal toxicity. Despite dose adjustment to renal function, the patient suffered acute kidney injury most likely of drug-toxic origin with nephrotic syndrome and combined glomerular and tubular damage. The ocular surface findings improved under the intensified local therapy and the patient achieved a significant increase in visual acuity with complete regression of the MECs and corneal staining over time. (Fig. 5) Additionally, OSDI® improved to 17. Thus, the topical therapy was adjusted to preservative-free hydrocortisone eye drops once a day, ciclosporin eye drops once a day and ganciclovir ointment at night. Preservative-free artificial tears were taken on demand.

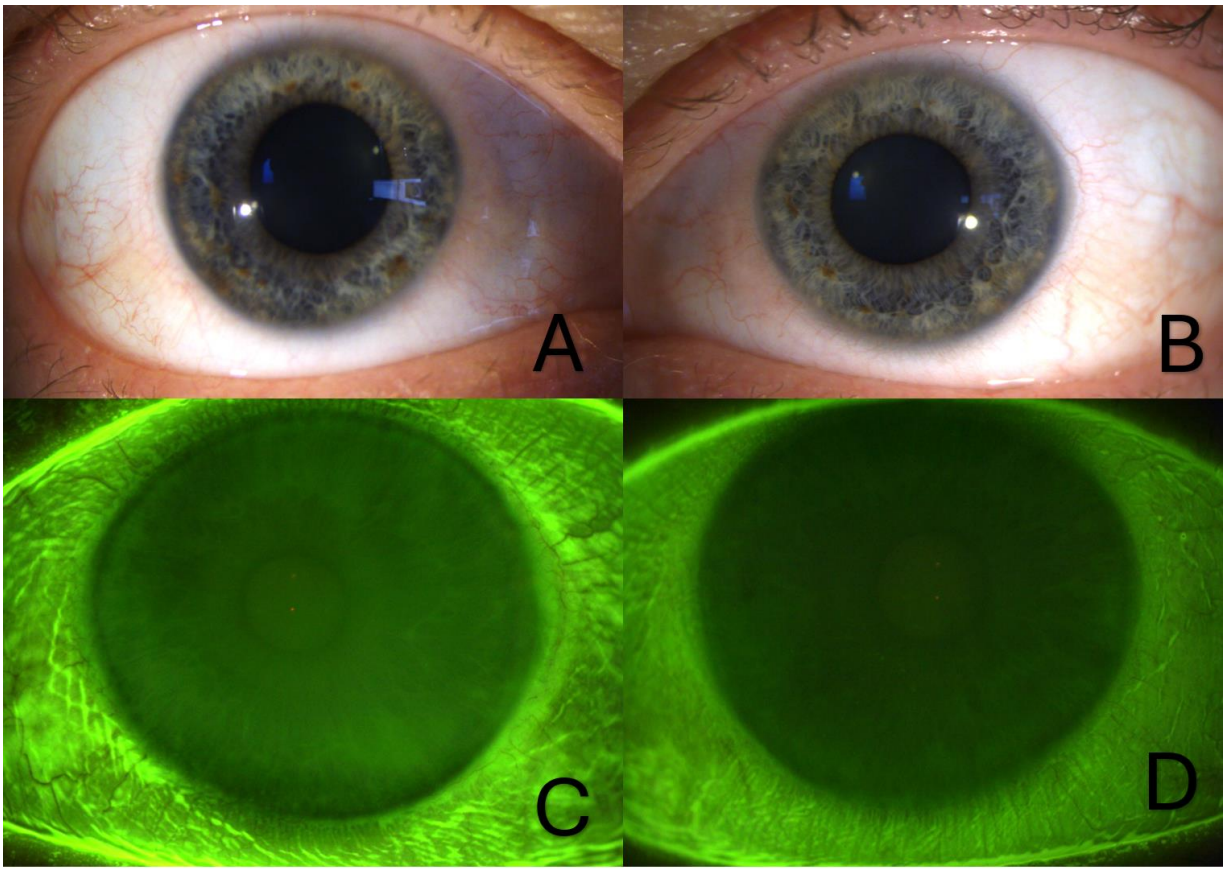

Figure 5 Upper pictures show the right (A) and left (B) eye at last control and 6 months after AMT. There were no more MECs and the corneal and conjunctival fluorescein staining was significantly improved (C right and D left eye).

Discussion

Like other herpesviruses, HSV-1 establishes lifelong infections in the host by becoming latent in neurons and occasionally reactivating. These recurrences lead to viral shedding in both symptomatic and asymptomatic individuals. The persistence and recurrence of HSV in otherwise healthy individuals are largely due to the numerous virulence factors, which have evolved to evade the host's antiviral responses. Herpes viruses can develop resistance to antiviral therapy, making it difficult to successfully treat severely affected patients. Immunosuppressed patients after aHSCT represent a vulnerable patient cohort with an increased risk of severe and life-threatening complications of these infections.

In the case of multimorbid patients, dose adjustments to antiviral therapy are often necessary. Due to the proven phenotypic resistance to acyclovir, in this case systemic antiviral therapy included multiple approaches including foscarnet, valaciclovir, cidofovir, the experimental drug pritelivir as a compassionate use and the exceptional use of personalized antiviral allogeneic T-lymphocytes. This so-called adoptive immunotherapy with antiviral T cells (AVT), which are

derived from healthy and seropositive donors, is a cutting-edge approach. It is regarded as a therapeutic breakthrough in refractory and severe viral infections, as these frequently occur in patients with primary immunodeficiencies or those undergoing aHSCT. The intensification of treatment underscores the extent of mucosal involvement and severity of HSV reactivation in our patient.

In the case described, the patient suffered from fulminant corneal involvement in addition to the most severe damage to the vulvar and oral mucous membranes.

The presented case describes on the one hand the latest antiviral therapy options, especially in cases of infection with resistant herpes viruses for the treatment of immunosuppressed patients and shows on the other hand three rare and impressive changes of the ocular surface.

First, our patient developed rapid, fulminant herpes keratitis with severe wound healing disorder. Conventional management was unsuccessful, so that further treatment was a challenge, also in consideration of the patient's poor general condition, who was still on the isolation ward. Wound healing was a key issue to improve the ocular surface of our patient with resistant HSV-1 keratitis. To eliminate the damaged epithelium and to aid healthy epithelial regeneration an amniotic membrane transplantation was performed after debridement. As we know, amniotic membrane works as a biological bandage with anti-inflammatory properties, which also reduces proinflammatory cytokines. Important reasons for improved epithelial regeneration are the epidermal growth factor (EGF) and keratocyte growth factor (KGF). (6) In a murine model AMT, which was followed by a decreased expression and activity of MMP-8 and -9, showed promising results in HSV stromal necrotizing keratitis. (7, 8) In our patient, AMT was successful despite the persistent viral load and there was no new ocular recurrence in the course of the disease.

Secondly, she developed severe chronic skin and oGVHD. The latter affects about 40-60% of patients after aHSCT. (9, 10) In its advanced stages, oGVHD is one of the most severe immunologically mediated diseases of the ocular surface and significantly and lastingly restricts the quality of life of those affected due to possible permanent loss of vision. Complications such as bacterial and mycotic ulceration or immunologically induced melting or even perforation of the cornea are a well-known risk in severe cases of oGVHD. (11) Fortunately, progression of oGVHD was prevented and controlled thanks to rapid initiation of treatment with topical steroids and ciclosporin. Of course, severe systemic GVHD with predominantly involvement of the skin was treated by the dermatologists and oncologists. For privacy reasons pictures of mucocutaneous herpetic involvement and skin lesions due to chronic GVHD are not displayed.

Thirdly, as a possible toxic reaction to the escalation of systemic therapy, microcyst-like changes in the corneal epithelium with a significant reduction in visual acuity and refractive shift were seen over the course of the disease. Under the established local therapy and multiple antiviral systemic medication changes, these regressed. Some antibody-drug conjugates (ADCs), as a class of cancer therapies, can be linked to corneal abnormalities. They consist of highly potent cytotoxins that can cause a range of side effects, with ocular toxicity being one of them. ADC-related keratopathy and MECs are still an area of ongoing research and exact mechanisms still need to be investigated. (12)

Conclusion

The remarkable course of our patient with therapy-resistant mucocutaneous HSV-1 infection highlights the close connection of the skin including mucocutaneous tissue and the eye. We emphasize the high need for increasing clinical awareness and the necessity of a multidisciplinary approach to manage such complex presentations of different organs effectively.

In severe herpetic keratitis AMT can support reestablishment of corneal integrity and enhance visual outcomes, but it should only be used additionally to antiviral therapy to manage the underlying HSV-1 infection. Moreover, close controls are mandatory to catch the window of opportunity of treating oGVHD before rapid progression in this vulnerable cohort.

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