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BRIEF REPORT

Corneal features in trastuzumab emtansine treatment: not a rare occurrence

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Abstract

Purpose Ado-trastuzumab emtansine (T-DM1/Kadcyla®;Genentech) is an antibody-drug conjugate used in the treatment of human epidermal growth factor receptor-2-positive metastasized breast cancer. Few studies report a spectrum of corneal changes in patients treated with this drug. Our aim is to specify the nature and prevalence of corneal features of T-DM1 treatment in order to formulate guidelines as to which findings necessitate systemic treatment cessation or dose reduction.

Methods We performed a cross-sectional, prospective study in all patients currently treated with T-DM1 or recently stopped in Ghent University Hospital, Belgium.

Results A total of 12 patients completed a full ophthalmic workup. Ten patients were currently using T-DM1, and two patients had recently (< 10 weeks) stopped treatment because of clinical non-response. Twenty eyes of 10 patients currently on T-DM1-treatment all exhibited coarse cystoid lesions to the deep corneal epithelial cells, primarily in the midperipheral area, both biomicroscopically and on confocal microscopy. The two patients who stopped treatment, displayed no corneal epithelial changes. Only three patients reported symptoms which were attributed to other ocular factors, likely not to be related to T-DM1 treatment.

Conclusions This case series shows that asymptomatic, low-grade corneal epithelial changes are hallmark features in T-DM1-treatment and should not alarm clinicians. These findings are relatively stationary, reversible and thus do not require ocular treatment or cessation of systemic treatment.

Keywords Ado-trastuzumab emtansine · T-DM1 · Breast cancer · Corneal toxicity · HER2

Abbreviations

ADC	Antibody-drug conjugate
BCVA	Best-corrected visual acuity
EGFR	Epidermal growth factor receptor
HER-2	Human epidermal growth factor receptor-2
RE	Right eye
LE	Left eye
T-DM1	Ado-trastuzumab emtansine

Introduction

In the field of medical oncology, ADCs are a rapidly evolving class of therapeutics. By linking a potent cytotoxic agent to a highly specific monoclonal antibody, specificity of targeting tumor cells is vastly increased, thus reducing systemic toxicity [1]. However, adverse effects have been shown to occur rather frequently before ADCs have reached their optimal therapeutic dose [2]. Ado-trastuzumab emtansine (T-DM1) has shown its efficacy in treating HER2-positive metastatic breast cancer and in general is well-tolerated [3]. Its selectiveness does not preclude the occurrence of toxicities, such as thrombocytopenia, increased liver transaminases and bilirubin, as well as cardiotoxicity [1]. Few reports have expanded on the specific ocular side-effects of T-DM1. Tsuda et al. were the first to acknowledge an extensive keratopathy in the treatment with T-DM1, necessitating discontinuation of treatment [4]. A vastly different phenotype of corneal toxicity was reported by Kreps et al. consisting of basal epithelial changes without the need for cessation of

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T-DM1 [5]. Randomized controlled trials on the subject in T-DM1 traditionally include little detailed information on the phenotype of ocular toxicity. We aimed to phenotype the specific corneal features of T-DM1 treatment in order to describe the prevalence of objective and subjective ocular findings and thus formulate guidelines as to which findings necessitate treatment discontinuation.

Methods

We performed a prospective, cross-sectional study in Ghent University Hospital (Belgium) from May 1 to September 30 2017. Inclusion criteria consisted of current T-DM1 treatment or recent (< 2 months) discontinuation of T-DM1 treatment. Patients with relevant ocular comorbidities preventing adequate assessment of T-DM1 ocular features were excluded. The following ocular examinations were performed: BCVA, slit-lamp examination with topical fluorescein, Schirmer I test (5 min; without topical anesthesia), Goldmann applanation tonometry, dilated fundoscopy (evaluating the retina and optic nerve) and in vivo confocal microscopy (Heidelberg Retina Tomograph II, Rostock Corneal Module). Visual acuity was measured using the Snellen eye chart at 6 m and noted as decimal fraction. Fluorescein-impregnated paper strips are wetted with a small drop of sterile unpreserved saline and lightly applied to the surface of the eye. Areas with superficial epithelial damage (both corneal and conjunctival) are typically highlighted by fluorescein when viewed with blue (cobalt) light filter. Schirmer I testing allows for quantification of tear production. When applied without topical anesthesia, it measures both the basal and reflex lacrimation. It was considered abnormal when wetting of the filter paper strip was less than 10 mm after 5 min. Confocal microscopy of the cornea allows for noninvasive, in vivo, high magnification analysis at the cellular level [6]. Both eyes of each patient were examined, and the cornea was scanned in 5 areas: the central cornea and the 4 quadrants. Specific grading systems for basal epithelial lesions are lacking. Therefore, the commonly used Oxford grading system—an adequate system for ocular surface staining—was modified in order to provide a semiquantitative assessment of epithelial lesions [7]. Ethics approval was obtained from the institutional Ethics Committee, and written informed consent was obtained from all included patients.

Results

A total of 12 patients were identified: 10 patients currently on T-DM1 treatment and 2 recently stopped. No patients were excluded, and all patients consented to participate in the study. Dose specifications and results of ocular work-up of the 10 patients on T-DM1 treatment are listed in Table 1. Mean age of these 10 patients was 55.6 ± 10.9 years. Prior treatment consisted of taxanes and trastuzumab (Herceptin®), next to a variety of other cytotoxic and monoclonal agents. Each of the 20 eyes revealed multiple small spheroid intra-epithelial opacities, mainly in the corneal midperiphery and lacking fluorescein staining (Figs. 1, 2). In all patients but one (patient nr 6), the intensity of epithelial opacities was very similar in both eyes. Hyperreflective cystoid bodies were invariably seen on in vivo confocal microscopy, primarily in the basal epithelium and wing cells with sparing of the superficial epithelium and the deeper corneal layers (Fig. 3). At the level of the subbasal nerve plexus, an increase in dendritic cells was remarked, mainly adjacent to higher intensity of opacities. The central

Table 1 Patient characteristics of 10 patients on T-DM1 treatment

Patient	Age (years)	Time on Kadcyla (cycles)	Cumulative dose (mg)	Ocular symptoms	BCVA		Grading scale		Schirmer I test (mm)	
					RE	LE	RE	LE	RE	LE
1	52	7	1630.8	–	1.0	1.0	2	2	2	5
2	59	22	4032.450	–	1.0	0.9	1	1	17	19
3	43	6	2038.68	–	1.0	1.0	2	2	11	21
4	35	31	6395.08	Dry eyes	1.0	0.8	2	2	7	9
5	65	74	14385.6	–	1.0	1.0	1	1	6	17
6	71	9	2397.6	Blurred vision	0.8	0.6	2	1	10	2
7	48	38	6154.74	–	1.0	1.0	1	1	2	5
8	60	34	7957.8	Blurred vision	1.0	0.9	2	2	15	14
9	61	5	1324.8	–	1.0	1.0	1	1	8	3
10	62	16	5101.2	–	0.9	0.9	2	2	4	1

Grading scale is according to the modified Oxford Scale for epithelial corneal lesions in each eye. Best corrected visual acuity (BCVA) is noted as a decimal fraction for each eye

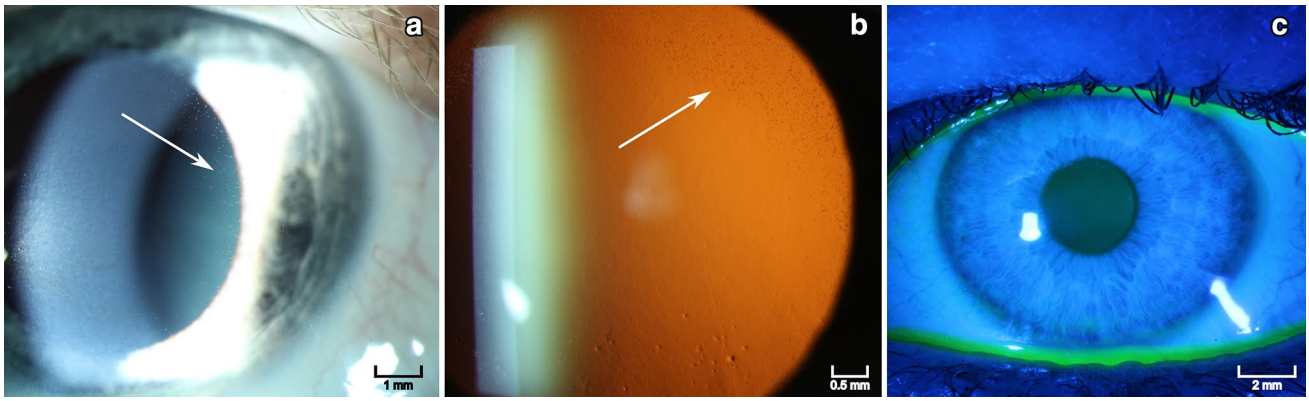

Fig. 1 Anterior segment photographs of the T-DM1-associated corneal microcystoid epitheliopathy. On **a**, the midperipheral lesions are evident using iris retroillumination, a slit-lamp technique which highlights corneal features by using the backscattered light from the iris (see arrow). Cystoid lesions are further highlighted by fundus retroillumination (**b**). A lack of fluorescein staining is characteristic (**c**)

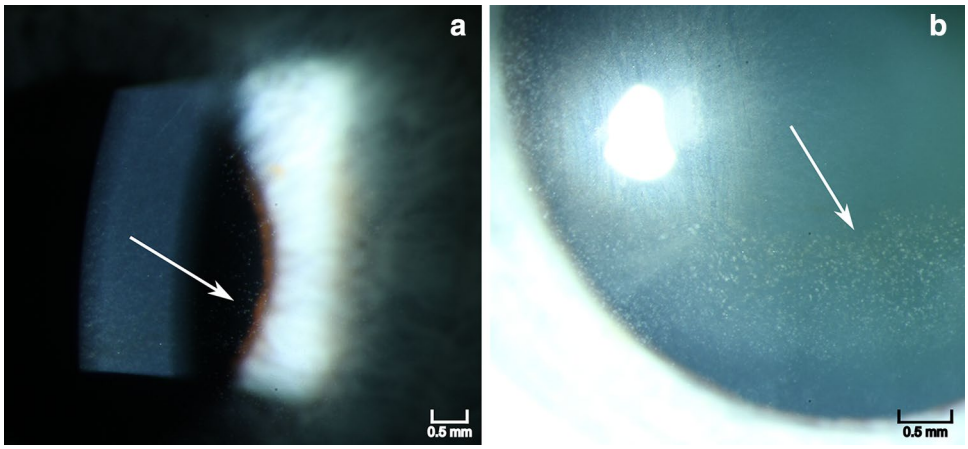

Fig. 2 Different grading of cystoid epitheliopathy. The intensity of the commonly used Oxford grading scale was used as a reference to assess the intensity of cystoid lesions in a semiquantitative manner. **a** Shows an example of a grade 1 epitheliopathy, whereas **b** features grade 2 epitheliopathy

cornea showed little to no hyperreflective foci, whereas the midperiphery in all quadrants exhibited lesions.

In all patients, intraocular pressure was within normal limits and dilated fundoscopy showed no abnormalities. Ocular symptoms were reported by 3 patients. Age-related lens opacities (cataract) were responsible for the moderate visual loss in two patients. The patient complaining of ocular dryness had a decreased Schirmer I score and fluorescein staining not related to the deeper corneal lesions. The 2 patients who had recently (2 months) stopped T-DM1 treatment due to progressive disease showed no signs of keratopathy. Of note, the previously published case [5] was followed up as well and showed no increase in corneal changes upon tapering of her autologous serum eye drops despite continuation of T-DM1 treatment. During the study period, no patients developed new ocular symptoms.

Discussion

Many ADCs target molecules, such as EGF receptors, that play an important role in corneal epithelial homeostasis. It should not come as a surprise that many ADCs are associated with some degree of corneal toxicity [8]. The cytotoxicity is likely to be related to intracellular accumulation of the active metabolite in normal corneal epithelial cells [9]. Ocular adverse events are commonly reported in nonspecific terms such as blurred vision and ocular dryness, without further details concerning its pathophysiology, management and need for cessation of ADC treatment [8]. As more and more ADCs are being developed and going into phase II and III studies, there will be an increasing need for both ophthalmologists and oncologists to understand

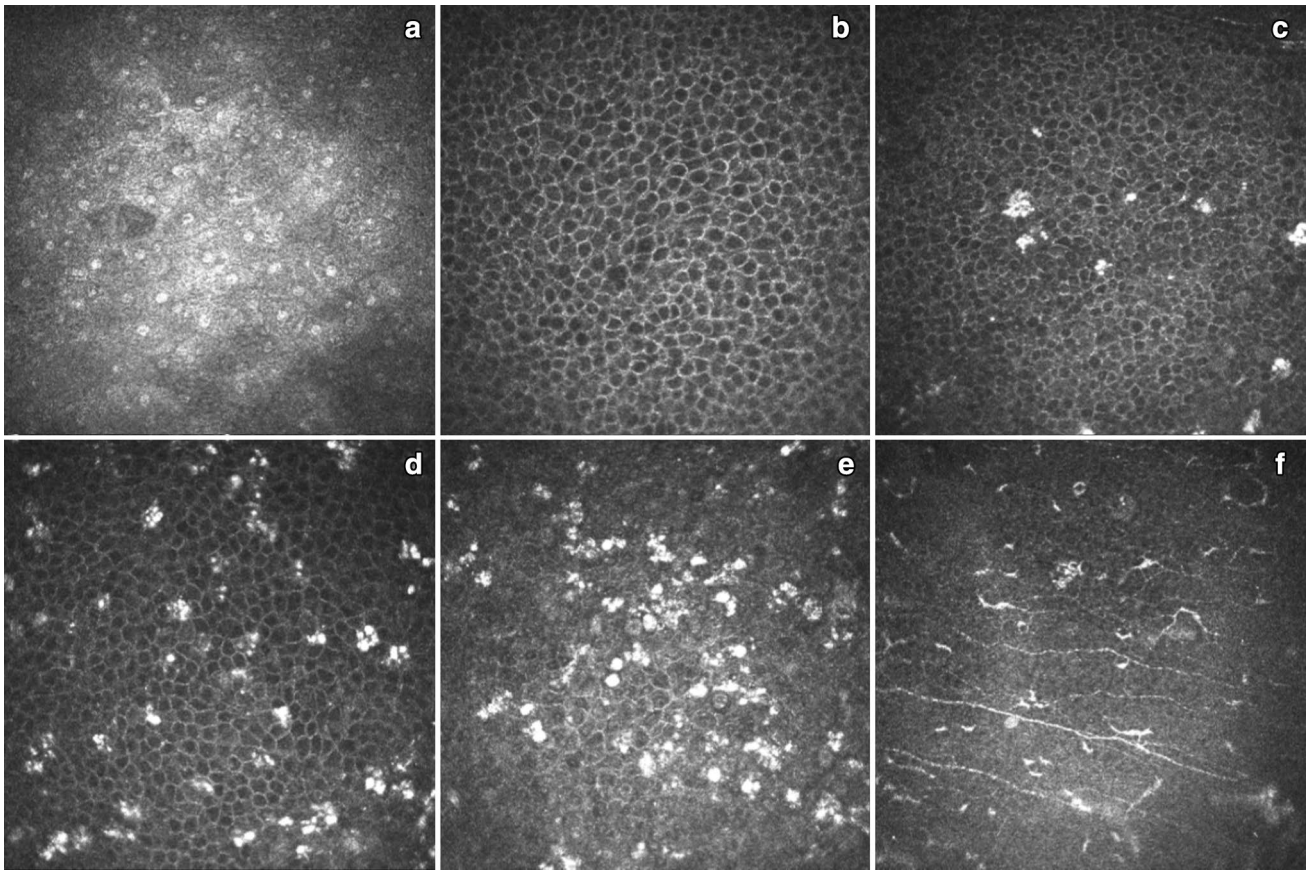

Fig. 3 In vivo confocal microscopy (all images are 400×400 µm). **a** and **b** Respectively show normal superficial corneal epithelium (depth 0 µm) and normal epithelial wing cells (depth 20 µm). **c** to **e** Show increasing density of hyperreflective lesions at the level of the wing cells in the corneal midperiphery (depth 30 µm). **f** (Depth 40 µm) demonstrates the increased presence of dendritic cells at the level of the subbasal nerve plexus

the various phenotypic expressions of corneal epithelial toxicity and to develop treatment strategies in order to enable continuation of these drugs without risking prolonged vision loss or ocular damage. Some of these ADCs, such as Trastuzumab duocarmazine (SYD 985; Synthon) and Sacituzumab Govitecan (IMMU-132; Immunomedics) already incorporate preventive measures in their treatment protocol [10, 11].

Epidermal growth factor is the primary endogenous growth factor responsible for corneal epithelial homeostasis [12]. Corneal epithelial stem cells are located at the limbus, the junction of the clear cornea and its surrounding conjunctiva. These stem cells migrate in a centripetal manner within the basal epithelial layers and further differentiate toward the superficial epithelium. Rapid cycling cells, such as the transient amplifying cells located within the basal cell layer of the corneal epithelium, are most sensitive to the actions of cytotoxins [13]. Four EGF receptors have been identified, amongst whom HER-2 is proven to be crucial to the migration of corneal epithelial cells [14, 15].

In peer-reviewed literature, 2 case reports have emerged on the specific topic of T-DM1 associated corneal toxicity [4, 5]. The level of toxicity differed substantially in both reported patients: one patient had extensive superficial corneal toxicity necessitating treatment discontinuation, whereas the other reported case only featured asymptomatic basal epithelial spheroid opacities. The findings of this study indicate that the basal epithelial spheroid opacities reported in the latter are highly common in patients on T-DM1 treatment. In all patients, there was a preponderance for the corneal midperiphery whereas the central cornea was clear. The transient amplifying cells in the corneal periphery display some of the characteristics of stem cells, who tend to have long cell cycles and thus are less vulnerable to the effects of cytotoxins [13]. This epitheliopathy has a very specific phenotype: rather than targeting the most superficial layer of the corneal epithelium, it is mainly the basal epithelial cells that show low-grade toxic changes without influencing visual acuity or causing ocular symptoms. We do not believe these opacities to represent substance deposition as no deposits were seen on confocal microscopy. The

hyperreflective lesions are likely to represent necrotic cell matter. There is also an increased presence of dendritic cells surrounding the opacities, further supporting the hypothesis of ADC-associated corneal toxicity with a low-grade local inflammatory response.

We had opted to treat our first case of T-DM1-related corneal epitheliopathy with autologous serum drops in order to prevent an increase of lesions in the assumption that these lesions were a rare occasion of toxicity [5]. During follow-up of this patient, we gradually tapered the autologous serum treatment and detected no change to the opacities. The patient remained asymptomatic and continued her T-DM1 treatment. We therefore did not initiate any topical treatment in the 10 patients included in this study as they were asymptomatic in terms of the basal epithelial findings and the lesions did not threaten the visual acuity (as they are not located centrally, disturbing the main visual axis). During the course of the study, none of the patients developed ocular symptoms despite continuation of their T-DM1 treatment. Interestingly, we have not observed the much more severe phenotype as reported by Tsuda et al. [4]. These authors described a severe corneal epitheliopathy, consisting of extensive changes to the superficial corneal epithelium with marked visual loss and need for treatment cessation [4]. Contrary to our findings of basal epithelial changes, this type of toxicity does appear to be a rare occurrence.

The 2 patients examined shortly following cessation of T-DM1 treatment showed no residual corneal changes, both in the basal and superficial epithelium. This suggests a self-limiting nature of the epithelial findings and the difference in phenotype to cetuximab-associated corneal epitheliopathy (an EGFR monoclonal antibody). This molecule causes typical corneal epithelial microcysts that progress from the basal to the apical layers to eventually desquamate [8].

We acknowledge a number of limitations to our study. As it was a monocentric study limited in time, the number of patients is rather low. However, the universal detection of similar lesions in all 20 eyes of examined patients supports a strong association between these basal epithelial findings and T-DM1 treatment. Secondly, densitometry (as available on the Pentacam HR Scheimpflug topography) would be a valuable device to further objectify and quantify the level of microcystic changes to the basal epithelium. It allows for detailed assessment of the level of backward scattering of light induced by various corneal layers, as measured in different concentric circles. Unfortunately, this module was unavailable to our department at the time of the study.

In conclusion, our findings support that asymptomatic low-grade corneal basal epithelial changes are hallmark features in T-DM1 treatment and should not alarm clinicians. These findings are relatively stationary, reversible, and thus do not require ocular treatment or cessation of systemic treatment. This association is important both to ophthalmologists and medical oncologists to be aware of, so as not to erroneously discontinue life-saving treatment.

Data availability The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The authors declare that the experiments comply with the current laws of the country in which they were performed (Belgium). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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