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Case Report

A Case of Corneal Melting in a Patient with HER2-Positive Breast Cancer

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Corneal melting · Trastuzumab · Immunotherapy · Cornea

Abstract
Trastuzumab is the cornerstone treatment for HER2-positive breast cancer. While ocular side effects are more commonly described after the use of the antibody-drug conjugate ado-trastuzumab emtansine, we here describe corneal melting in a 79-year-old patient after three cycles of trastuzumab monotherapy. Signs and symptoms persisted with subsequent trastuzumab cycles. The patient showed improvement after treatment with intense lubrication, topical antibiotics, and topical steroids. After tapering of steroids, there was recurrence of epitheliopathy after subsequent trastuzumab treatment, which subsided upon restarting topical steroids. Finally, the patient was kept on a low-dose topical steroid regimen which prevented further epitheliopathy during the next trastuzumab cycles.

Introduction

In medical oncology, highly specific monoclonal antibodies have emerged as an important therapeutic agent on the market. Trastuzumab is a recombinant humanized monoclonal antibody against human epidermal growth factor (EGF) receptors [1]. EGF receptors, also called ErbB proteins, belong to subclass I of the superfamily of receptor tyrosine kinases and consist of four proteins: EGF receptor ERBB1/HER1, ERBB2/Neu/HER2, ERBB3/HER3, and ERBB4/HER4 [2].

In 20–25% of human breast cancers, HER2 is overexpressed. This is associated with aggressive tumor growth and poor prognosis [1]. Down-regulation of HER2 downstream

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signaling cascades inhibits the proliferation and survival of human EGF receptor (HER2)-dependent tumors. Chemotherapy with anti-HER2-directed treatment, trastuzumab with or without pertuzumab, is currently used as a standard treatment for early HER2+ breast cancer [3, 4].

EGF receptors and HER2 specifically are expressed on the corneal, limbal, and conjunctival epithelia with a preference of superficially differentiated surface epithelia [5, 6]. Epithelial growth factor receptors are considered to be a major factor in corneal wound healing because of the stimulation of proliferation and migration of epithelial cells [5].

While ocular effects of trastuzumab monotherapy are not commonly observed in human subjects [3], trastuzumab is often used in an antibody-drug conjugate called ado-trastuzumab emtansine. With this antibody-drug conjugate, corneal toxicity is a well-known side effect [7, 8]. Ocular toxicity is also well known with other antibody-drug conjugates, and the adverse effects most commonly occur at the ocular surface and cornea [9]. This case report describes a patient who experienced corneal toxicity after monotherapy treatment with trastuzumab.

Case Report

Our patient is a 79-year-old Caucasian male diagnosed with a differentiated ductular adenocarcinoma of the left breast stage 3 (cT2 CN0 cM0, HER2+). The patient underwent a mastectomy with sentinel lymph node procedure. Given amplification of the HER2/Neu oncogene and node negative status, the patient was eligible for adjuvant chemotherapy and trastuzumab for 1 year. Paclitaxel was started as chemotherapy but needed to be discontinued after 7 weeks because of suspected herpetic encephalitis without sequelae.

After paclitaxel was discontinued, treatment with trastuzumab was started with administration of the drug every 3 weeks. After 3 cycles of trastuzumab, the patient presented with a unilateral foreign body sensation and a profound visual acuity loss. Corneal melting of the right eye was observed by the treating ophthalmologist. The patient was treated with topical antibiotics, topical antivirals, lubrication, and steroids. This topical treatment was combined with oral valaciclovir and doxycycline. A polymerase chain reaction (PCR) test was performed which was negative for varicella-zoster virus (VZV) and herpes simplex virus (HSV).

After a consecutive round of treatment with trastuzumab, a second round area of corneal melting emerged. Given the poor response to the previously prescribed treatment, the patient was at this time referred to our tertiary clinic.

The patient presented with a best-corrected visual acuity (BCVA) of 20/400 (Snellen) in the right eye and a BCVA of 20/25 in the left eye. Biomicroscopy revealed a mild conjunctival injection with prepupillary epitheliopathy with profound corneal thinning in the right eye (Fig. 1a, b). In the left eye, biomicroscopy was normal. Both eyes showed a normal intraocular pressure of 10 mm Hg. Fundoscopy showed no abnormalities. Treatment consisting of topical antibiotics (ofloxacin twice daily), topical antivirals (ganciclovir ophthalmic gel 0.15% 3 times daily), artificial tears (every hour), and steroids (dexamethasone eyedrops once daily) was continued at this time. A second corneal swab for PCR analysis was negative for HSV and VZV. The patient showed no improvement with this treatment. Given the second negative PCR test, topical and oral antivirals were tapered and discontinued.

Because of the correlation in time and the known relationship of trastuzumab emtansine with corneal damage, the consecutive dose of trastuzumab was postponed by 1 week, after consultation with the treating oncologist. During this period of delay, no further corneal thinning was observed, and an improvement in ocular complaints and BCVA (20/150) was noted. Considering the positive evolution of signs and symptoms, treatment with trastuzumab was continued.

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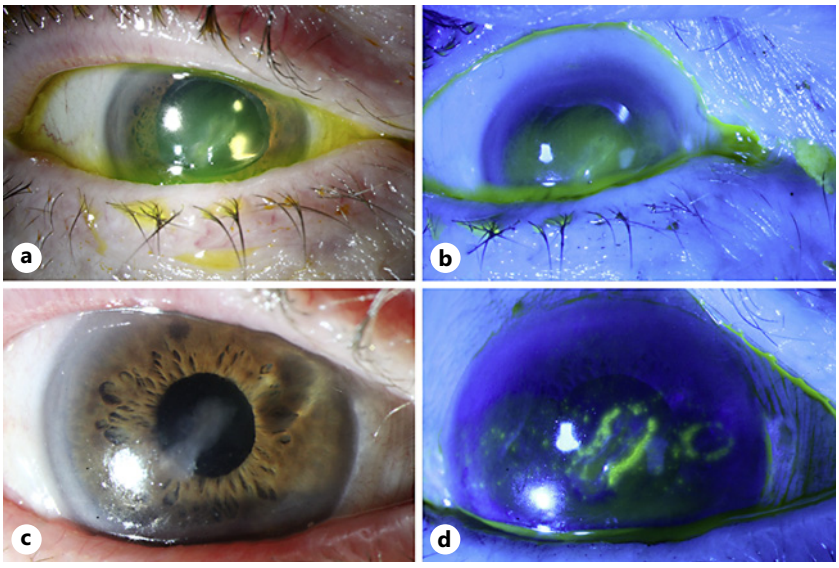

Fig. 1. Anterior segment photography in the right eye. **a** Notice oblique prepupillary corneal melting at presentation. **b** Notice epitheliopathy over the zone with corneal melting at presentation. **c** Notice known oblique prepupillary corneal thinning and a new round zone of thinning nasally 8 weeks after presentation. **d** Notice epitheliopathy (staining) at the borders of the corneal thinning using blue light and fluorescein dye 8 weeks after presentation.

Two days after the next round of trastuzumab, our patient presented with increased ocular discomfort. Biomicroscopy identified a recurrence of corneal epitheliopathy at the edges of the corneal thinning (Fig. 1c, d). Anterior segment optical coherence tomography showed an intact epithelium with stromal melting in two separate zones (Fig. 2).

In response to these observations, the patient was treated with intense lubrication (artificial tears every other hour and vitamin A ointment 3 times daily) and topical antibiotics combined with topical steroids (dexamethasone/chloramphenicol 3 times daily). Upon treatment, a reduction in activity of the edges of the corneal thinning was observed. The antibiotic drops were discontinued, and the steroid drops were tapered. Trastuzumab treatment was restarted, and the patient was monitored closely. After tapering of topical steroids, a new zone of epitheliopathy without corneal thinning was observed in the left eye 4 days after trastuzumab treatment. The topical antibiotics combined with topical steroids (dexamethasone/chloramphenicol 3 times daily) were restarted, and the epitheliopathy resolved. Topical steroids were continued in a low dose (dexamethasone once daily) in both eyes to prevent recurrence. Further, follow-up of the patient showed no progression of the corneal lesions while on trastuzumab treatment, and no recurrences occurred after completing the treatment.

Discussion

In this report, we describe a patient with corneal stromal melting and overlying epitheliopathy most likely caused by trastuzumab monotherapy, considering the temporal relationship. Trastuzumab is a monoclonal antibody against human EGF receptors used in the treatment of HER2-positive breast cancer.

HER2 (ERBB2) is a cell membrane protein within the receptor tyrosine kinase family [7]. The presence of epithelial growth factor receptors in the corneal epithelium and their positive

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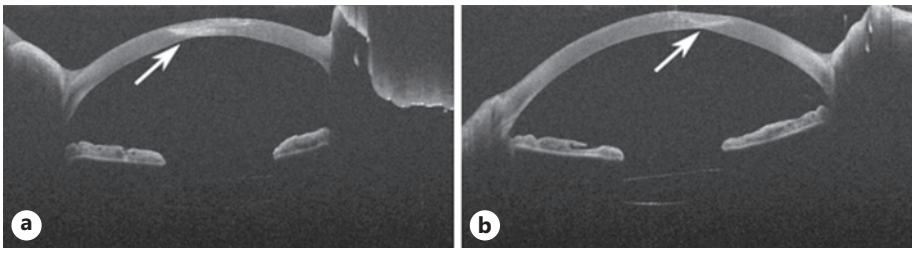

Fig. 2. Anterior segment OCT 8 weeks after presentation. **a** Notice prepupillary stromal melting with intact overlying epithelium. **b** Notice nasal zone of stromal thinning with intact overlying epithelium.

effect on proliferation and migration of corneal cells are well known [5, 10]. The receptors are involved in regulating cell proliferation and differentiation [7]. Because of this relationship, epithelial growth factors are deemed essential in corneal healing [10]. In most adult tissues, HER2 is expressed at low levels in epithelial cells. However, in the corneal and conjunctival epithelium, there is a stronger expression of HER2 compared to other epithelial tissues [10]. In vitro depletion of functional HER2 in human corneal epithelial cells results in retarded chemotactic cell migration. Systemic administration of trastuzumab was proven effective in prevention of the corneal neovascularization in a rat model [7, 11], underscoring the importance of functional HER2 in corneal function.

The relationship between corneal epithelial changes and antibody-drug conjugate trastuzumab emtansine treatment has already been described [7, 8]. Corneal lesions were also described in other antibody-drug conjugates [8].

A literature review identified one case where corneal ulceration was observed in a patient treated with trastuzumab monotherapy. In this study, it was hypothesized that trastuzumab-induced HER2 inhibition may cause impaired turnover of the corneal epithelium [10]. Alternatively, the corneal damage could be immunologically mediated by antibody-dependent cell cytotoxicity. Recently, Kafa et al. [12] published a case of bilateral marginal corneal infiltration upon combined treatment with trastuzumab, pertuzumab, and docetaxel.

In our patient, we observed corneal melting confirmed by optical coherence tomography imaging. Surprisingly, we saw an intact epithelium with underlying stromal thinning. Given the mechanism of action of trastuzumab, it is unexpected that an overlying zone of intact epithelium would be present. Clinically, however, epitheliopathy was clearly visible at the edges of the stromal thinning. To further explain this observation, the exact pathophysiological mechanism remains to be elucidated. Further, follow-up of our patient showed no progression but also no resolution of corneal lesions. We acknowledge some possible confounding factors in establishing a causal relationship between corneal melting and trastuzumab treatment. First of all, our patient was previously treated with paclitaxel. Corneal epithelial lesions and limbal stem-cell deficiency during paclitaxel treatment have been described previously [12]. However, in our patient, paclitaxel was discontinued 1 month before the first signs of corneal toxicity. It is however possible that prior treatment with paclitaxel increased the patient's sensitivity to trastuzumab-mediated toxicity. Second, corneal melting in this patient could be secondary to herpetic keratitis. However, corneal swab for PCR analysis was performed twice and came back negative for both HSV and VZV. Additionally, despite using topical and oral antivirals, a second zone of corneal melting emerged, while tapering antivirals did not influence the clinical course. In favor of a causal relationship between corneal melting and trastuzumab therapy is the obvious temporal relationship between the trastuzumab treatment cycles and the appearance of ocular signs and symptoms. Eventually, we were able to continue trastuzumab treatment through strict follow-up and the use of low-dose topical corticosteroids.

In conclusion, we report the first case of suspected trastuzumab-related corneal stromal melting. Patients experiencing ocular discomfort and/or vision loss, while receiving trastuzumab immunotherapy, should be referred for urgent ophthalmological examination. Discussion with the patient and medical oncologist is important because if ocular side effects can be controlled with corticosteroids, it may be in the patient's best interest to continue potentially life-saving treatment.

Statement of Ethics

The Ethics Committee in University of Ghent (Commissie voor Medische Ethiek) approved this case report (reference 2022-050). All procedures conducted in this study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Deborah Peeters examined the patient and wrote and edited the manuscript. Dimitri Roels wrote and edited the manuscript. Hannelore Denys and Melissa Vereecken reviewed the manuscript.

Data Availability Statement

All data generated and analyzed for this case are included in the article. Further inquiries can be directed to the corresponding author.

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