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J Case Rep Images Opthalmol 2025 Jul-Dec;8(2):1–4.
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CASE REPORT PEER REVIEWED | OPEN ACCESS

An ocular twist to cancer therapy: Pseudomicrocysts and myopic shift linked to trastuzumab emtansine

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ABSTRACT

A 49-year-old woman with a diagnosis of HER-2 positive breast cancer on trastuzumab emtansine (Kadcyla) therapy developed symptoms of dry eye, and blurry vision bilaterally. Subjective myopic shift was noted and slit lamp examination revealed bilateral corneal epithelial pseudomicrocysts. These ocular symptoms emerged within weeks of Kadcyla initiation, improved with drug cessation and recurred on reintroduction, suggestive of keratopathy secondary to antibody-drug conjugate (ADC) toxicity. Management included intensive ocular lubrication, close follow-up, and reassurance of the temporality of symptoms with ADC use. Antibody-drug conjugate therapy was continued as tolerated. This case highlights the potential for reversible keratopathy, including pseudomicrocysts and myopic shift associated with trastuzumab emtansine.

Keywords: Antibody-drug conjugate, Corneal pseudomicrocysts, Myopic shift, Trastuzumab emtansine

How to cite this article

Bird FH, Sahoo B, Oskam J. An ocular twist to cancer therapy: Pseudomicrocysts and myopic shift linked to trastuzumab emtansine. J Case Rep Images Opthalmol 2025;8(2):1–4.

Article ID: 100046Z17FB2025

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Received: 15 June 2025
Accepted: 28 July 2025
Published: 26 August 2025

doi: 10.5348/100046Z17FB2025CR

INTRODUCTION

Antibody-drug conjugates (ADCs) are targeted cancer therapies that link cytotoxic payloads to monoclonal antibodies, associated with malignant cell antigen [1]. While designed for on-target toxicity, ADCs frequently cause ocular surface adverse events (AEs). Reported symptoms include blurred vision, tearing, dry eye, and refractive change while slit lamp examination findings include punctate keratopathy and characteristic corneal pseudomicrocysts. Lindgren et al. found that 3 in 11 ADCs have been implicated in the formation of pseudomicrocysts (incidence of 41–100%); notably a further six reported other ocular surface adverse events. The pathogenesis may involve ADC uptake by corneal epithelial cells—either “on-target” (if the target antigen, e.g., HER2, is present on normal epithelium) or more commonly “off-target” payload uptake via nonspecific endocytosis [1].

Trastuzumab emtansine (Kadcyla, T-DM1) is a HER-2 targeting ADC, approved for HER2 positive metastatic breast cancer. Pivotal human trials on the use of Kadcyla revealed ocular side effects of under 10% of patients (mostly dry eye) and no formal ocular toxicity warning was issued. Real world studies however have noted frequent corneal epithelial changes. A cross-sectional prospective study of T-DM1 patients in Belgium saw 20 eyes of 10 patients all develop cystoid lesions to the deep corneal epithelial cells, primarily in the midperipheral region [2]. Tsuda et al. [3] also reported bilateral corneal epithelial abnormalities originating at the limbus in a single patient on long-term Kadcyla, improving after treatment cessation. These findings clearly suggest that Kadcyla is implicated in limbal epithelial injury, likely via affecting the limbal stem cell population [3]. This present case illustrates clearly the temporal relationship of these lesions to T-DM1 dosing, and a more unusual feature of myopic refractive shift.

CASE REPORT

A 49-year-old female with a history of ER+/PR+/HER2+ (triple positive) carcinoma of the right breast was referred by medical oncology with new-onset visual symptoms. Her treatment included neoadjuvant chemotherapy (docetaxel, carboplatin, trastuzumab), mastectomy, axillary dissection, and radiotherapy. Due to residual disease, she commenced trastuzumab emtansine (Kadcyla; IV 3.6 mg/kg every three weekly) and tamoxifen.

Following the third infusion of Kadcyla, she noted insidious blurry vision in both eyes and symptoms of dry eye bilaterally. She noted clearer near vision without glasses and blurred distance vision, suggestive of a myopic shift. In concurrence with ocular symptoms, multigated acquisition (MUGA) showed a significant decrease in her cardiac ejection fraction prompting medical oncology to temporarily withhold oncologic treatment. Importantly from an ocular perspective, her symptoms of dry eye and subjective myopic shift regressed at this time. Kadcyla treatment was ultimately reinstated three months later as systemically appropriate, which correlated with a recurrence of her adverse ocular effects. There is no history of contact lens use, no previous ocular problems or eye surgery.

On examination, unaided visual acuity was 6/6 in each eye. Pupils were equal and reactive to light with no afferent defect. Intraocular pressures were recorded as normal bilaterally. Slit-lamp biomicroscopy revealed small, gray/white, round epithelial inclusions in the mid-peripheral cornea of both eyes, greater in prevalence OS (left eye) (Figures 1 and 2). These appeared to be at the level of the basal epithelium. The corneal epithelium was otherwise intact, free of edema or haze and with minimal fluorescein staining. Conjunctivas were white bilaterally and anterior chambers were deep, quiet, and free of flare. Dilated fundus examination of each eye was unremarkable, and spectral-domain OCT of the macula and optic nerve were free of pathology. These findings, of bilateral mid-peripheral corneal pseudomicrocysts without intraocular inflammation in the context of Kadcyla therapy were indicative of an antibody-drug-conjugate (ADC) associated keratopathy.

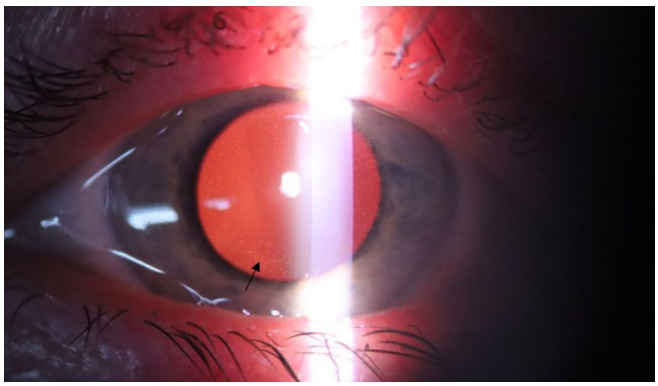

Figure 1: Slit-lamp image of the left eye showing multiple mid-peripheral corneal pseudomicrocysts under retro-illumination. These lesions appeared shortly after Kadcyla infusion.

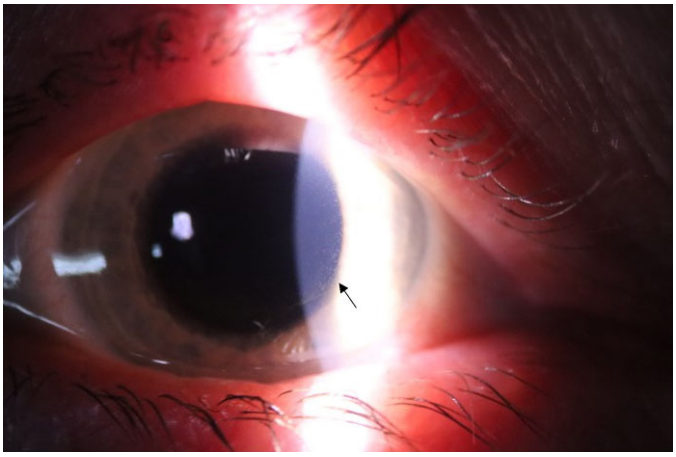

Figure 2: Slit-lamp image of the right eye showing these tiny gray/white epithelial inclusions in the basal epithelium of the cornea.

The patient was treated conservatively with lubricating eye drops. Given her tolerable symptoms and the importance of continued cancer therapy, Kadcyla was maintained at full dose. The oncology team was advised to monitor for ocular symptom progression.

DISCUSSION

This case describes a classic example of ADC-induced corneal toxicity. The insidious onset of symptoms after initiating Kadcyla infusions and the temporal relationship with cessation, strongly support a causal relationship. This has been described in other ADCs. Trials of Belantamab mafodotin (Blenrep) saw 72% of patients developed blurred vision secondary to corneal pseudomicrocysts [4], leading to dose delays of up to 47% and dose reductions in 23%.

Corneal pseudomicrocysts likely arise from cytotoxic effects on the corneal epithelium, especially the limbal stem cell region. Although HER2 expression on corneal epithelium is minimal, “on-target” effects are possible. More commonly, “off-target” uptake via nonspecific endocytosis leads to apoptosis of epithelial cells. Histologic studies confirm cyst-like inclusions within the basal epithelium, initially in the periphery and potentially migrating centrally with ongoing exposure [5].

Patients with corneal pseudomicrocysts often report ocular irritation or dry eye and blurred vision [1], such as seen in this case. The refractive change has also been reported elsewhere. Lindgren et al. explain that peripheral corneal lesions can cause the central cornea to flatten and induce hyperopia, while more central lesions have the opposite effect. Interestingly in this case, microcysts were predominantly (mid)peripheral with the predominant refractive shift being myopic. It could be said that the lesions may have migrated prior to examination/imaging or that subclinical central edema may have caused the

myopic shift. Regardless, it is more evidence that ADC related keratopathy can induce refractive change.

Diagnosis ultimately lies in recognition of the clinical picture; a history of ADC use, with new onset refractive change, identification of the pathognomonic corneal pseudomicrocysts, temporality with drug initiation, with or without other ocular surface AEs. Anterior segment spectral domain OCT can be useful in clarifying the etiology of epithelial cysts (whereby true cysts will appear hypo-reflective, pseudocysts hyper-reflective) however this was not necessary in this case. It is important to comment that a complete ocular examination is required to rule out other causes of this symptomatology.

Recommended management is focused on symptom control and persistence with cancer therapy when symptoms are mild [1]. Lubricants and cold compresses may offer relief; however, they do not prevent pseudomicrocyst development. Evidence for prophylactic or therapeutic steroid use is inconclusive. The most effective intervention remains dose modification of the ADC, though this must be balanced against oncologic benefit. Symptom regression typically occurs within weeks to months of drug cessation.

CONCLUSION

Bilateral corneal pseudomicrocysts in conjunction with refractive change and other ocular surface adverse events, should prompt consideration of toxicity in patients receiving ADCs. This case highlights that even in the absence of moderate to severe symptoms, slit lamp examination and other investigations may be warranted to detect these changes early. Mild ocular side effects may not necessitate discontinuation of therapy, but recognition and documentation are essential to guide future management. Further research is needed to optimize prevention and treatment strategies for ADC-induced keratopathy.

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Author Contributions

Felix Henry Bird – Conception of the work, Design of the work, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Baswati Sahoo – Conception of the work, Acquisition of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Joshua Oskam – Conception of the work, Acquisition of data, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.