Corneal perforation in breast cancer patients receiving combination chemotherapy with pertuzumab/trastuzumab targeted therapy: a case report

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Case presentation

A 67-year-old woman with an unremarkable ophthalmic history presented to the ophthalmology department with a 'gush of fluid' and reduced vision in her left eye, from 6/20 in the Snellen test (recorded in 2023 at a private hospital), to hand movements, after her sixth cycle of combination chemotherapy (paclitaxel and carboplatin) and targeted therapy (combined pertuzumab/trastuzumab in a subcutaneous injection) for metastatic breast cancer. She had experienced bilateral eye discomfort and intermittent epiphora since the start of her combined chemotherapy/targeted therapy. She denied any topical medication use such as steroid or nonsteroidal anti-inflammatory drugs.

Clinical findings revealed left upper lid swelling and conjunctival injection, a central corneal perforation with iris plugging and a flat anterior chamber in the patient (Fig 1a). Her right eye showed mild punctate epithelial erosions in keeping with mild dry eye disease; there was no sign of corneal melting. Corneal sensation in both eyes was intact. Schirmer's test was not performed at first presentation due to the emergent nature of the condition.

Viral and bacterial conjunctival swabs were taken and cyanoacrylate glue and a bandage contact lens were applied immediately to the left eye corneal perforation (Fig 1b). Viral and bacterial cultures were negative. Blood tests for rheumatoid factor, anti–extractable nuclear antigen screen and anti–nuclear antigen to look for an autoimmune cause were also negative.

The combined therapy was discontinued immediately and the patient underwent a multilayer amniotic membrane transplant along with anterior chamber reformation to restore globe integrity while awaiting a subsequent corneal graft transplant (Fig 2a). One month later, with her ocular condition temporarily stabilised, she underwent radical mastectomy for her breast cancer. No further adjuvant chemotherapy was administered.

Five months later, the patient's general health had stabilised. With the development of

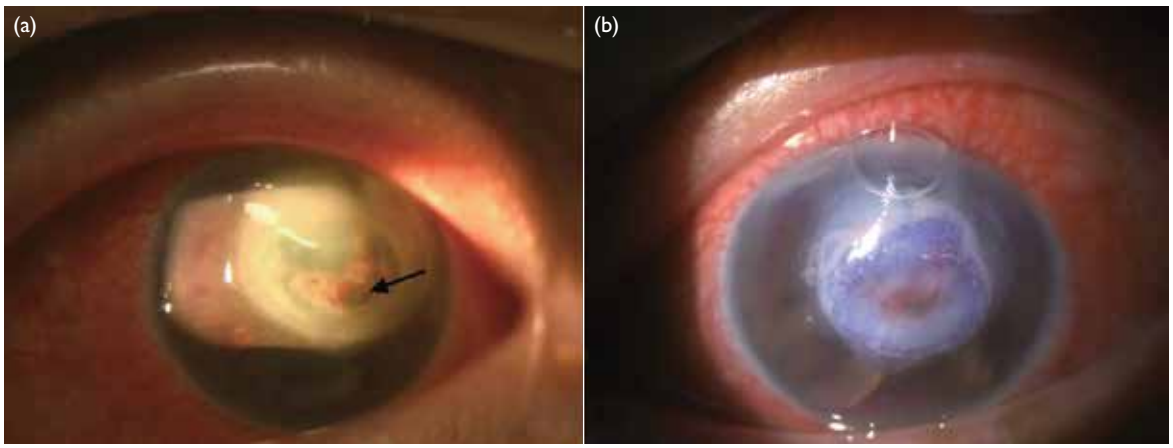

FIG 1. (a) Left eye central corneal perforation (arrow) with iris plugging and flat anterior chamber. (b) Left eye cyanoacrylate glue (purple) surrounding the perforation site, with bandage contact lens on top

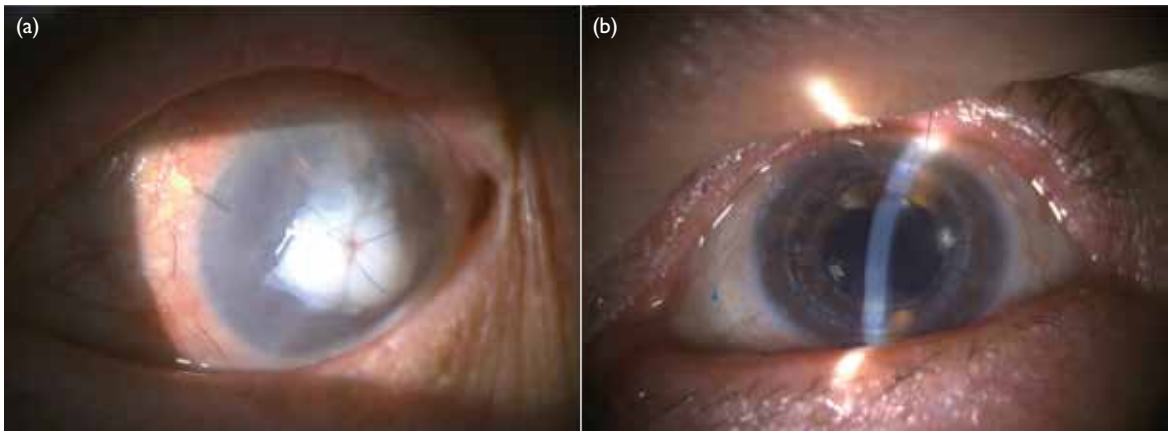

FIG 2. (a) Left eye post multilayer amniotic membrane transplant, anterior chamber reformed and air bubble seen. (b) Left eye 2 months post combined penetrating keratoplasty, extracapsular cataract extraction and intrascleral haptic fixation of intraocular lens. The graft was clear

an intumescent cataract in her left eye, a triple procedure of penetrating keratoplasty, extracapsular cataract extraction and intrascleral haptic fixation of intraocular lens (due to zonulysis) was performed.

Fortunately, the patient's left eye visual acuity recovered to 6/20 in the Snellen test and was expected to further improve following suture removal (Fig 2b). The patient did not develop any further corneal erosion or melting in either eye after drug discontinuation. Her right eye was well at the latest follow-up and showed no sign of ocular surface disease. The most recent Schirmer's test in both eyes was within normal limits.

Discussion

The top differential aetiologies in this case were herpetic, neurotrophic, or drug-induced. Although herpetic stromal keratitis does not usually present at such a late stage, it can occur in immunocompromised patients. Nonetheless, since the patient denied a history of herpetic infection and viral swabs were negative, this diagnosis was unlikely. Neurotrophic keratopathy was also excluded on the basis of bilaterally normal corneal sensation. In light of the timing of symptom onset following the chemotherapy/targeted therapy, combined with a negative history of ocular surface disease, we suspect the corneal perforation was most likely drug-induced.

Carboplatin has not been reported to cause ocular surface side-effects although it has been rarely linked to optic neuropathy, retinal ischaemia, and pigmentary maculopathy.[1] Paclitaxel is a taxane-based chemotherapeutic agent and aside from cystoid macular oedema, has also been associated with scintillating scotoma, photopsia, dry eye, conjunctivitis, and limbal stem cell deficiency.[1,2]

Human epidermal growth factor receptor 2 (HER2) antibody drugs, pertuzumab and trastuzumab, are used in the treatment of HER2-positive breast cancer and were administered concurrently with chemotherapy in our patient. Given the presence of HER2 receptors on the ocular surface and lacrimal glands, ocular surface disease can occur as a side-effect.[2] The ocular side-effects of trastuzumab have been well documented and include conjunctivitis, dry eye, and marginal keratitis.[2,3] Nonetheless there have been limited case reports of aggressive corneal melting associated with trastuzumab monotherapy.[4] Pertuzumab has been associated with epiphora and conjunctivitis, but to date there have been no reported cases of corneal melting or perforation linked to pertuzumab or the specific combination formulation of pertuzumab/trastuzumab targeted therapy. We hypothesise that the concurrent use of taxane-based chemotherapy, known for its ocular surface side-effects, in combination with HER2-targeted therapy, may have contributed to the aggressive corneal melting observed in this case. Nonetheless the possibility that the HER2 combination therapy (pertuzumab/trastuzumab) alone could have been responsible cannot be ignored.

It is of note that this new formulation drug is given as a fixed-dose subcutaneous injection of 1200 mg pertuzumab and 600 mg trastuzumab for one loading dose followed by 600 mg pertuzumab and 600 mg trastuzumab every 3 weeks for maintenance. The conventional intravenous dose of trastuzumab is based on body weight (8 mg/kg loading, 6 mg/kg maintenance). It is difficult to compare doses since the administration routes differ, although a phase 3 trial showed that the serum trough level of the drug is slightly lower when administered subcutaneously.[5]

Therefore, the severe ocular presentation in this case could not be explained by a higher dosage or bioavailability of the anti-HER2 drugs since bioavailability would be lower with the subcutaneous route.[5]

Furthermore, in the phase 3 trial on this new formulation combination targeted therapy drug, it was also administered along with taxane chemotherapy (similar to our patient), a common regimen in hormone receptor positive breast cancer.[5] All side-effects were recorded but no ocular surface side-effects were reported.[5] Hence, the potential ocular surface side-effects are not listed in the package insert for this relatively new combined subcutaneous formulation of pertuzumab and trastuzumab.

In conclusion, our patient experienced unilateral vision loss due to corneal perforation while undergoing treatment with a combination of chemotherapy and targeted therapy. Among the drugs administered, paclitaxel and trastuzumab are most frequently associated with ocular surface side-effects, and their concurrent use may have contributed to the severity of the presentation. Patients receiving combined taxane chemotherapy and HER2-targeted therapy—including newer formulations such as combined subcutaneous pertuzumab/trastuzumab—should be warned about potential ocular surface complications. Early referral for ophthalmic evaluation is recommended at the onset of any ocular symptoms to prevent serious, vision-threatening outcomes.

Author contributions

Concept or design: ALW Li, VWM Ho.
Acquisition of data: ALW Li, VWM Ho, DHT Wong.
Analysis or interpretation of data: ALW Li, VWM Ho.
Drafting of the manuscript: ALW Li, VWM Ho.
Critical revision of the manuscript for important intellectual content: All authors.
All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, KKW Li was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

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Ethics approval

The study was approved by the Central Institutional Review Board of Hospital Authority, Hong Kong (Ref No.: IRB 2024-707). The patient provided written informed consent for publication of this case report and unidentifiable information and images.

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