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Management of severe capecitabine-induced corneal toxicity

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ABSTRACT

Purpose: To describe the clinical presentation and management of severe capecitabine-induced corneal toxicity.
Observations: A 71-year-old woman presented with severe bilateral vision loss. Four months earlier, capecitabine was initiated for a metastatic invasive ductal carcinoma. Biomicroscopy revealed bilateral whorl-like corneal epitheliopathy accompanied by metaplasia, keratinization and subepithelial fibrosis. After consulting the treating oncologist, capecitabine treatment was discontinued. Initially, a non-surgical approach was adopted and intensive topical dexamethasone treatment was applied. Despite capecitabine discontinuation and topical steroid treatment, visual acuity progressively declined. Bilateral corneal scraping and bandage contact lens fitting was performed. This resulted in significant improvement of visual acuity, corneal surface regularity and quality of life.
Conclusion and importance: We report the first case of severe visual impairment due to capecitabine-induced corneal toxicity. Early corneal scraping, especially when confronted with profound vision loss, may yield better outcomes compared to relying on spontaneous recovery after capecitabine discontinuation. Patients experiencing ocular discomfort and vision loss, while receiving capecitabine therapy, should be referred for semi-urgent ophthalmological examination.

1. Introduction

Chemotherapy-induced ocular complications pose unique challenges in the management of cancer patients. Capecitabine, a fluoropyrimidine carbamate, is a widely used antimetabolite agent for pretreated breast cancer, with a complex metabolism involving conversion to active 5-fluorouracil (5-FU) in tumor cells. Despite capecitabine's ocular side effects being exceptional, they can have a major impact on quality of life. This case report describes a patient who experienced significant vision loss due to corneal toxicity after treatment with capecitabine.

2. Case report

Our patient is a 71-year-old Caucasian female diagnosed with breast cancer fifteen years ago. She underwent a tumorectomy with sentinel lymph node procedure. The pathology report demonstrated a grade 2 invasive ductal carcinoma, estrogen and progesterone positive, HER2 negative, a pT1c N0 tumor according to TNM classification. She was treated with endocrine therapy (tamoxifen followed by exemestane) and radiotherapy. Seven years later, bone metastases were identified in the lumbar vertebrae, therapy was changed to anastrozole and denosumab in combination with local radiotherapy. One year later, liver metastases were detected on PET-CT, leading to a switch in therapy to chemotherapy consisting of antracyclines and cyclophosphamide. Subsequently, she was treated with palbociclib/fulvestrant for 3 years, followed by two regimens of chemotherapy: paclitaxel and cyclophosphamide-methotrexate. Eventually, capecitabine was initiated at a dose 1000 mg/m2 bid, given for 14 days on a 21-day cycle due to progressive liver metastases. After 4 cycles, the dose was interrupted for an extra week because of a grade 2 hand-foot syndrome. After the symptoms cleared, capecitabine was restarted at a lower dose.

Four months after starting capecitabine, this patient was referred to our tertiary ophthalmology clinic with significant vision loss, more pronounced in the right eye. There was no history of ocular disease, surgery or medication use. The patient sporadically wore soft contact lenses. Her treating ophthalmologist noticed corneal changes 3 weeks

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prior to referral and initiated treatment consisting of topical dexamethasone eye drops 6 times a day, tobramycine eye drops 3 times a day and artificial tears 6 times a day. At presentation, best-corrected visual acuity (BCVA) was limited to counting fingers (<20/400) in the right eye and 20/63 in the left eye. Biomicroscopy revealed severe whorl-like epitheliopathy with subepithelial fibrosis reaching from the superior half of the cornea to the center (Fig. 1), more pronounced in the right eye, as well as cataract in both eyes. Intraocular pressure was 18 mmHg in the right eye and 15 mmHg in the left eye. Fundoscopy showed no abnormalities. Anterior segment ocular coherence tomography (OCT) showed a hyperreflectivity of the corneal epithelium in the superior and prepupillary region, while stroma and endothelium showed no abnormalities (Fig. 2). After consultation with the treating oncologist, capecitabine treatment was discontinued. Since spontaneous improvement of signs and symptoms six to eight weeks after discontinuation of capecitabine had been described previously,[1] a non-surgical approach was chosen. Treatment consisting of topical preservative-free dexamethasone eye drops 6 times a day, dexamethasone gel at night and artificial tears 6 times a day was continued.

One week later, our patient presented with a BCVA of 20/400 in the right eye and 20/200 in the left eye. *In vivo* confocal microscopy (IVCM) showed a hyperreflectivity of the basal epithelial cell layer, with a normal appearance of the corneal stroma and endothelium (Fig. 2). A corneal scraping was performed in the affected area of the right eye. A bandage contact lens was placed and topical ofloxacin eye drops 3 times a day were added. Direct microscopic examination of the epithelium collected by corneal scraping showed signs of parakeratotic keratinization (Fig. 3). There were no signs of inflammation or viral inclusions. One week after corneal scraping BCVA in the right eye improved to 20/32. Eight weeks after discontinuing capecitabine, BCVA in the left eye fluctuated between 20/50 and 20/80. Biomicroscopy showed persisting epithelial metaplasia with subepithelial fibrosis, more pronounced in the superior half of the cornea. Corneal scraping in the left eye was performed and a bandage contact lens was placed. Eight weeks after corneal scraping, BCVA had improved to 20/40.

Since corneal scraping resulted in a more regular corneal surface, biometry could be performed with higher accuracy and cataract surgery was scheduled for the right eye. Three weeks after uncomplicated cataract surgery, BCVA in the right eye was however limited to 20/200. This suboptimal BCVA could be attributed to the irregularity of the corneal surface, despite treatment with topical dexamethasone 3 times a day and preservative-free artificial tears 6 times a day. One month after new bandage contact lens fitting in the right eye, BCVA had improved to 20/25 again. Six weeks after cataract surgery in the left eye, BCVA had also improved to 20/25. Unfortunately, six months after cataract surgery our patient passed away due to cancer progression.

3. Discussion

In this report, we describe a patient with severe corneal toxicity associated with capecitabine use. Capecitabine, a fluoropyrimidine carbamate, is an antimetabolite agent indicated for the treatment of pretreated breast cancer. It is administered orally as a prodrug and metabolized to fluorouracil (FU) in three steps. The enzyme responsible for the last step of drug activation is thymidine phosphorylase. This shows greater concentration in tumor cells where it produces

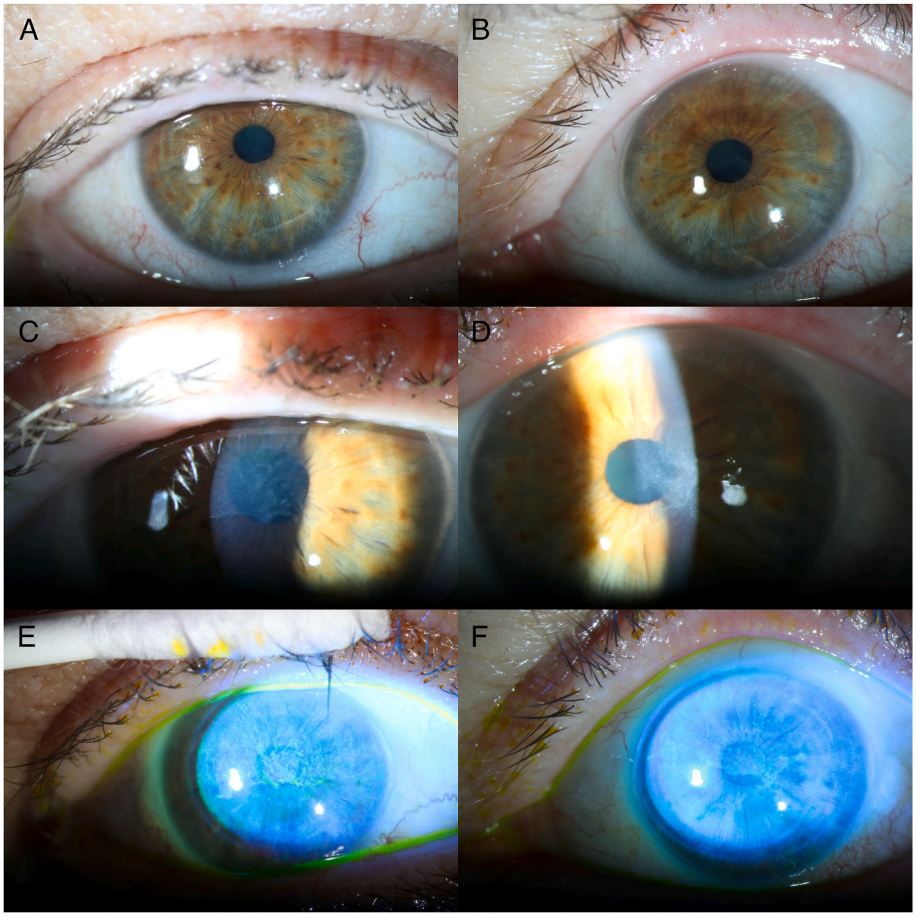

Fig. 1. Anterior segment photography at presentation. Notice macroscopically normal-appearing anterior segment of the right eye (A) and left eye (B). Slit lamp examination showing corneal epitheliopathy and subepithelial fibrosis in the right (C) and left eye (D). Fluorescein dye illustrating whorl-like epitheliopathy in the superior half of the cornea, more pronounced in the right eye (E) compared to the left eye (F).

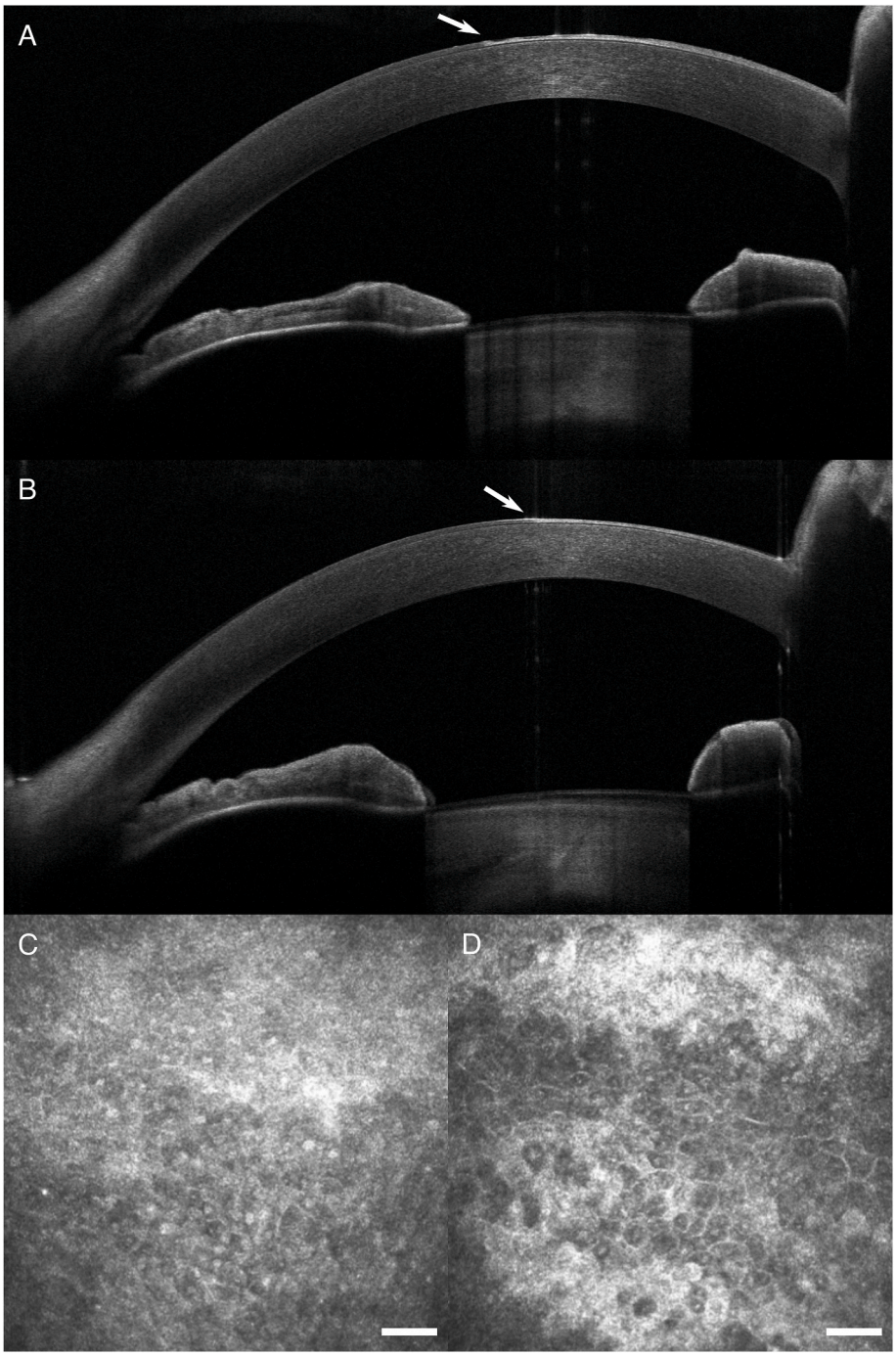

Fig. 2. Anterior segment OCT at presentation in the right eye (A) and the left eye (B). Notice hyperreflectivity of the corneal epithelium in the superior half of the cornea and sparing of the inferior half (white arrows highlight transition zone). *In vivo* confocal microscopy showing hyperreflectivity at the basal epithelial cell layer in the right eye (C) and the left eye (D), compatible with the clinically evident subepithelial fibrosis (scale bar = 50μm).

pharmacological active levels of 5-FU, ultimately behaving as tumor-selective drug.[1,2] 5-FU is a pyrimidine analog that inhibits cellular proliferation by being incorporated in the DNA or RNA promoting cytotoxic effect within cells.[3,4] The exact mechanism of capecitabine-induced corneal toxicity is not fully understood. Among the various pyrimidine analogue drugs, capecitabine may particularly affect corneal epithelial cells and keratocytes, possibly due to formulation characteristics that increase the blood concentration of 5-FU.[5] An electron microscopic study on rats revealed an altered histological structure of the cornea with a deformation in the epithelial layer after 30 days of treatment with capecitabine. The study showed epithelial thinning and desquamation of the cells.[6] Similar results were observed in capecitabine corneal toxicity in dogs.[7] Hereditary genetic variants may affect a drug's pharmacokinetics or pharmacodynamics and account for differences in treatment response and adverse events among patients. The dihydropyrimidine dehydrogenase (DPD) enzyme is required to convert 5-FU to 5-fluorodihydrouracil. Deficient DPD activity due to mutations in the DPYD gene may lead to increased toxicity from 5-FU as well as capecitabine.[8] Genetic testing in our patient revealed two functional DPYD-alleles, resulting in no increased risk of developing adverse events.

Few cases of capecitabine-induced ocular side effects have been

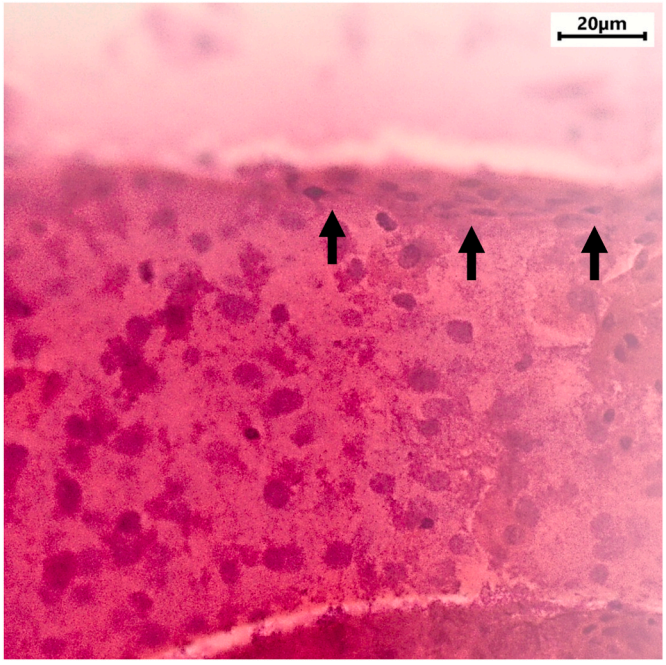

Fig. 3. Direct microscopic examination of the epithelium collected by corneal scraping. Notice signs of parakeratotic keratinization (arrows).

described, including corneal toxicity,[1,2] cicatricial ectropion[9] and unexplained vision loss.[10] Two patients described by Waikhom B. et al. (2000) experienced vision loss to 20/40. In both patients superficial punctate keratitis and multiple white, granular subepithelial corneal deposits were noticed. Six to eight weeks after cessation of capecitabine, there was corneal clearing and a return to normal vision. Di Staso F. et al. (2021) described a patient with epithelial and anterior stromal corneal defects resembling a whorl pattern, however no decline in visual acuity was reported. Regression of the epithelial and stromal defects was observed 10 days after discontinuation of capecitabine and addition of autologous blood-derived serum eye drops. Ferrari et al. (2010) described a case of capecitabine-associated peripheral sensory neuropathy assessed using IVCM.[11] However, in our patient IVCM did not identify anomalies in morphology and number of corneal nerves.

In our case, a conservative approach was initially adopted. However, despite intensive topical dexamethasone treatment, the patient's visual acuity dropped to counting fingers (<20/400) in the right eye and 20/200 in the left eye. A corneal scraping in the right eye was conducted one week after capecitabine discontinuation and one week after corneal scraping BCVA improved to 20/32. Similarly, in the contralateral eye, where no improvement was observed eight weeks after capecitabine discontinuation, a corneal scraping was performed. In both eyes a bandage contact lens was fitted to reduce postoperative pain and to improve corneal healing. Both interventions led to notable improvements in visual acuity and corneal surface regularity, albeit with residual subtle subepithelial fibrosis. The management of our patient was based on the knowledge that mechanical debridement of conjunctiva-like epithelium is a valid, simple and effective treatment in patients with partial limbal stem cell deficiency, as it encourages the denuded area to be resurfaced with corneal epithelial cells.[12] Prompt treatment of capecitabine-induced corneal toxicity, combined with cataract surgery, allowed our patient to gain back binocular BCVA of 20/25. This dramatically improved her quality of life, which she was able to enjoy for the last six months of her life.

In conclusion, we report the first case of severe capecitabine-induced corneal toxicity, including epithelial metaplasia, keratinization and subepithelial fibrosis. Patients experiencing ocular discomfort and vision loss, while receiving capecitabine therapy, should be referred for semi-urgent ophthalmological examination. Especially when confronted with profound vision loss, early corneal scraping and bandage contact lens fitting may yield better outcomes compared to relying on spontaneous recovery after capecitabine discontinuation.

Patient consent

The patient's legal guardian consented to publication of the case orally. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

CRediT authorship contribution statement

Mathieu Heyvaert: Writing – original draft, Investigation. **Hannelore Denys:** Writing – review & editing. **Jo Van Dorpe:** Writing – review & editing. **Dimitri Roels:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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