Case report

Rapidly progressive *streptococcus dysgalactiae* corneal ulceration associated with erlotinib use in stage IV lung cancer

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**Abstract**

**Purpose:** To present a unique case of *streptococcus dysgalactiae* keratitis with progression to corneal perforation and endophthalmitis, in the setting of epidermal growth factor receptor inhibitor (erlotinib) therapy for advanced non-small cell lung cancer.

**Observations:** An 89-year-old female with non-small cell lung cancer on erlotinib presented with corneal perforation due to infectious keratitis. Microbial cultures grew *streptococcus dysgalactiae*, a virulent pathogen known to affect immunocompromised patients that has not been previously described to cause infectious keratitis.

**Conclusions and Importance:** Epidermal growth factor receptor inhibitor therapy can result in significant ocular complications including dry eyes, epithelial keratopathy, non-healing abrasions, infectious keratitis, and rarely, corneal melting and perforation. These side effects can predispose patients to aggressive infections with rare organisms, highlighting the importance of understanding the ocular side effects of systemic chemotherapeutic agents.

**1. Introduction**

Erlotinib (Tarceva; Genentech, Inc, San Francisco, CA), an epidermal growth factor receptor (EGFR) inhibitor, is used in the treatment of non-small cell lung cancer and has been associated with various ocular side effects. Most commonly, EGFR-inhibitor use has been associated with a dysfunctional tear film and blepharitis. Less frequently, trichomegaly, trichiasis, eyelid rash and hyperemia, and epithelial defects have been noted to occur.

*Streptococcus dysgalactiae* (a Lancefield Group C or G streptococcal organism) has been reported to cause a range of infections in soft tissue and skin, as well as meningitis, septic arthritis, and endocarditis. An increasing incidence of *streptococcus dysgalactiae* subspecies equisimilis has been reported in recent years. Infections are most commonly found in elderly patients with systemic comorbidities and skin breakdown. There are reports of associated endogenous and post-surgical endophthalmitis in the literature, but to our knowledge, there are no confirmed reports of bacterial keratitis or corneal ulceration as a result of *streptococcus dysgalactiae*.

In this report, we present an unusual and severe case of *streptococcus dysgalactiae* corneal ulceration with rapid progression to corneal melt and perforation leading to endophthalmitis in a patient using EGFR inhibitory therapy for metastatic lung cancer.

**2. Case report**

An 89-year-old female presented to the emergency room with two days of vision loss, redness, purulent discharge, and a corneal ulcer in the right eye. Medical history was significant for stage IV non-small cell lung cancer, treated with erlotinib for the last two years. She had been previously treated for worsening blepharitis, trichiasis, punctate epithelial keratopathy in both eyes, and inferior stromal thinning in the right eye. Long-term management included lid hygiene, cyclosporine 0.05%, and artificial tears in both eyes. Six months prior, she was treated for a small corneal infiltrate in the right eye associated with a poorly healing epithelial defect that eventually resolved. Final vision was 20/100 in the right eye, after which the patient was lost to follow-up for several months.

Her presenting visual acuity was count fingers at three feet in the right eye and 20/80 in the left eye. Slit-lamp biomicroscopy of the right
eye revealed a purulent corneal ulcer with perforation and iris prolapse (Fig. 1). The stromal defect was successfully closed with cyanoacrylate glue and an overlying bandage contact lens was placed. The chamber re-formed and hourly fortified vancomycin and tobramycin drops were started, along with oral vitamin C and doxycycline. Microbiological studies revealed gram-positive cocci in chains on gram stain, and cultures subsequently grew *Streptococcus dysgalactiae* (Group C streptococcus) (Fig. 2), detected by Matrix-Assisted Laser Desorption-Ionization Time-of-Light Mass Spectrometry (MALDI-TOF MS), resistant to clindamycin and erythromycin (Table 1).

Table 1

| Antibiotic     | Minimum Inhibitory Concentration | Sensitivity |
|----------------|----------------------------------|-------------|
| Ceftriaxone    | 0.25                             | Susceptible |
| Levofloxacin   | 2.0                              | Susceptible |
| Penicillin     | 0.125                            | Susceptible |
| Vancomycin     | 0.38                             | Susceptible |
| Clindamycin    | 256                              | Resistant   |
| Erythromycin   | 256                              | Resistant   |

On day two, visual acuity was hand motion. A persistent corneal perforation was noted, with interval worsening of the corneal infiltrate, requiring re-application of cyanoacrylate glue and a bandage contact lens. On day three, visual acuity had worsened to no light perception. The patient had signs of clinical worsening including moderate periorbital edema and erythema, slight proptosis, limitation of extraocular movements, diffuse chemosis, profound conjunctival injection with purulent discharge, and a 3-piece intraocular lens haptic visible in the shallow anterior chamber (Fig. 3). Gentle B-scan ultrasonography demonstrated choroidal effusions and vitreous debris suggestive of early endophthalmitis (Fig. 4). Given the suspicion for orbital extension, computed tomography of the orbits with and without contrast was performed, which showed extensive soft tissue swelling with few areas of fat-stranding within the orbit. Due to the aggressive nature of the disease and the immunocompromised status of the patient, the decision was then made to initiate broad-spectrum intravenous antibiotics for endophthalmitis with early orbital cellulitis. Blood work revealed negative peripheral cultures and a mild leukocytosis of 11,400 cells per mL.

Over the course of several days, vision remained at no light perception. Although the periorbital inflammation improved slightly, the cornea continued to show signs of a worsening infiltrate involving 360° of the limbus, with continued corneal melt and diffuse purulence underneath the bandage contact lens. Considering the lack of visual potential and an increasingly disorganized and infected globe, as well as the concern for orbital extension, the decision was made to proceed with enucleation. At the time of surgery, there was near complete corneal melt, with notable prolapse of the 3-piece intraocular lens

![Fig. 1. Corneal stromal melt with an approximately 1.5 mm by 1.5 mm perforated defect, with uveal tissue plugging the defect (right eye).](image1)

![Fig. 2. Blood agar with colony growth after 24 hours, identified as *Streptococcus dysgalactiae* (group C streptococcus).](image2)

![Fig. 3. At day 2, periorbital edema and erythema, trichiasis and trichomegaly, chemosis and diffuse conjunctival injection, diffuse purulence with an enlarging corneal infiltrate, with an intraocular lens haptic visible in a shallowed anterior chamber.](image3)

![Fig. 4. B-scan ultrasonography (right eye) demonstrating mixed serous and hemorrhagic choroidal effusions with loculated debris in the limited residual vitreous cavity, suggestive of progression to hypotony and early endophthalmitis.](image4)
through Descemet’s membrane.

Fig. 7. Hematoxylin and Eosin stain of the corneal specimen, excised intraoperatively, demonstrating a corneal stromal abscess with posterior rupture through Descemet’s membrane.

Fig. 5. An intraoperative photo of the right eye. After gentle removal of the bandage contact lens, near total corneal melt was observed with diffuse purulence, friable and chemotic conjunctiva, with disorganized ocular contents and a 3-piece intraocular lens visible extruding from the anterior chamber.

Fig. 6. Gram stain of an intraocular specimen after evisceration, demonstrating diffuse necrotic material, neutrophil infiltration, and numerous gram-positive cocci (arrow).

In patients using erlotinib or other EGFR inhibitors, our report highlights the importance of regular follow up, symptom monitoring, and prompt referral to an ophthalmologist when an infectious process is suspected. Furthermore, the rapid progression of *Streptococcus dysgalactiae* keratitis warrants particular attention, as its detection may herald a deterioration in corneal integrity that portends significant ocular morbidity.

3. Discussion and conclusion

Epidermal growth factor receptor, a transmembrane glycoprotein, is expressed in epithelial tissue throughout the body. Constitutive expression takes place in the basal epithelial cells throughout the cornea and limbus. Thus, its function is integral for corneal epithelial cell proliferation, and plays a crucial role in corneal wound healing and epithelial integrity. EGFR inhibitors are used in the management of solid malignancies such as pancreatic, basal cell, and colorectal carcinomas, as well as non-small cell lung cancer. Several case series and reports have documented the ocular side effects associated with this class of medication, which vary from chronic dry eyes, epithelial keratopathy, trichiasis, trichomegaly, and blepharitis, to more severe conditions such as non-healing abrasions, ulcers, infectious keratitis, and rarely, corneal melting and perforation. This constellation of findings may present with an indolent course without an obvious immediate association with the use of an EGFR inhibitor, leading to difficulties in management.

*Streptococcus dysgalactiae* (Group C streptococcus) is an emerging pathogen, presenting with an assortment of infectious presentations similar to *Streptococcus pyogenes*. Disease ranges from skin and soft tissue infections, to necrotizing fasciitis, streptococcal toxic shock syndrome, endocarditis, and meningitis. *S. dysgalactiae* has been linked to underlying malignancy and an immunosuppressed state, with infection more prevalent among elderly patients with skin breakdown. Infections related to this microorganism are increasing in prevalence, although they have rarely been reported with ocular manifestations. The reports of ocular involvement include endogenous endophthalmitis and panophthalmitis from bloodstream infections in the setting of endocarditis or abscesses, and post-surgical exogenous endophthalmitis after small-incision cataract surgery. Notably, as in our patient, intraocular cases of *S. dysgalactiae* are difficult to treat and have a poor visual prognosis.

Epithelial defects, stromal thinning, corneal melt, and perforation have all been reported in the setting of erlotinib use, requiring penetrating keratoplasty in the most severe cases. Given the timing of our patient’s worsening ocular surface disease (stromal thinning, blepharitis, and trichiasis eventually complicated by infectious keratitis and perforation), we theorize that these changes were causally related to the continued inhibition of EGFR with long-term erlotinib use. After our review of the literature, no reports of infectious keratitis secondary to *S. dysgalactiae* were identified. This supports the unique nature of the present case, which began as an infectious keratitis with rapid progression to endophthalmitis. In the setting of long-term exposure to erlotinib, with its known ocular side effect profile, we suspect that this extremely virulent organism presented itself as an opportunistic infection in a predisposed eye.
novel immune therapies continue to provide new avenues of treatment for systemic diseases, ophthalmologists must become aware of the potential for ocular side effects and complications associated with these drugs. Future research within ophthalmology would benefit from an increased focus on optimal management and prevention in collaboration with our colleagues across medical specialties.

4. Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

Declaration of competing interest

The following authors have no financial disclosures (EKS, SA, KI, JP, CA, KE, DDR, RG). All authors attest that they meet the current ICMJE criteria for Authorship.

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