



Case report

Bilateral acute simultaneous onset anterior uveitis presumed secondary to erlotinib: A report of two cases



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ABSTRACT

Purpose: To report two new cases of presumed erlotinib-associated bilateral acute simultaneous-onset anterior uveitis effectively treated with topical steroids.

Observations: Two patients were referred to the uveitis clinic with bilateral acute simultaneous onset, anterior uveitis six weeks after starting the chemotherapeutic agent erlotinib. Frequent topical steroid were started and the inflammation responded swiftly and completely.

Conclusions and importance: Bilateral acute simultaneous onset anterior uveitis is a potential side effect associated with erlotinib use that has not been well described. Physicians should be aware of this potential association in patients with recent treatment with erlotinib who complain of blurred vision, photophobia, or redness of the eyes. In some cases, the inflammation responds well to topical therapy and medication can be continued.

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1. Introduction

Erlotinib, an orally administered epidermal growth factor receptor (EGFR) inhibitor, has gained widespread use in the treatment of patients with advanced EGFR mutant non-small cell lung carcinoma.¹ Erlotinib is indicated for the treatment of non-small cell lung cancer after failure of at least one prior chemotherapy regimen and is also a first-line adjunctive treatment for patients with locally advanced, unresectable, or metastatic pancreatic cancer. The safety and efficacy of these medications has been reported, and although they are generally well tolerated, EGFR inhibitors are associated with adverse effects, most commonly rash and gastrointestinal disturbances, including diarrhea, nausea, and lack of appetite.¹

The most common ocular adverse events reported with use of erlotinib are dysfunctional tear syndrome, blepharitis, eyelash changes, and corneal epithelial defects.² Bilateral acute onset anterior uveitis in association with erlotinib use as an additional adverse effect has only been described in two prior case reports.^{3,4}

Birnbaum and colleagues have described more common causes of non-granulomatous acute anterior uveitis with bilateral

simultaneous onset. In a report of 4288 new patients presenting to the Uveitis Service over a ten-year period, only 44 (1%) presented with simultaneous-onset non-granulomatous bilateral acute anterior uveitis. The most common etiology was post-infectious or drug induced uveitis (23 patients, 52%).⁵ Herein, we present two cases of bilateral acute simultaneous onset of uveitis secondary to systemic use of erlotinib, successfully treated with topical steroids.

2. Findings

2.1. Case 1

A 67-year-old Caucasian woman presented to the Uveitis Clinic with a two-week history of painless blurred vision at distance and near and floaters in both eyes. Her past medical history was notable for anxiety, chronic pain syndrome, and adrenal insufficiency.

Two years prior, she had been diagnosed with an EGFR positive primary non-small cell lung cancer after incidental discovery of a right lower lobe lung tumor during routine imaging. She underwent right lower lobectomy and lymph node dissection. There were no metastases on PET scan and no adjuvant chemotherapy was pursued. She was monitored for two years with screening CT scans. Six weeks prior to presentation she suffered repeat falls and painless jaundice. Repeat imaging revealed new bilateral lung nodules with metastases in the bone, liver, and pancreatic head. A

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biliary stent was placed and she was started on erlotinib 150 mg orally daily for recurrent EGFR positive non-small cell lung cancer.

Three weeks after starting erlotinib, she was hospitalized for persistent high fevers, diarrhea, and fatigue. During this hospitalization she developed blurred vision and floaters. Extensive laboratory and radiologic testing, including blood, urine, and stool studies, serial body CT, ERCP to evaluate stent function, and rheumatologic serologies failed to reveal an infectious etiology of the symptoms but showed marked improvement in the pulmonary, liver, pancreatic, and bony metastases. She was diagnosed with presumed tumor fever and discharged with acetaminophen. White blood cell counts shortly admission to the hospital and after discharged remained within normal limits at 6.2–9.5 k/microL. She presented to the ophthalmology clinic soon after discharge.

Best-corrected visual acuity was 20/30 in both eyes and intra-ocular pressures were normal. Ocular examination revealed diffuse small to medium sized keratic precipitates and extensive Koeppel nodules in the right (Fig. 1, arrow) and left eyes. The anterior chambers of both eyes had 3 + cell and 2 + flare. Gonioscopy revealed open angles without Berlin nodules or peripheral anterior synechiae, and posterior segment examination was unremarkable.

Antistreptolysin O titers, urine beta-2 microglobulin, ACE, lysozyme, QuantiFERON gold, RPR, FTA-ABS, and a chest X ray were negative. She was diagnosed with bilateral acute simultaneous onset anterior uveitis presumed secondary to erlotinib and treated with a topical ophthalmic steroid every 2 h. Inflammation resolved within three weeks. At one-year follow-up, she remained without evidence of ocular inflammation. Erlotinib was not interrupted or discontinued at any time.

2.2. Case 2

A 73-year-old Caucasian woman was referred by her primary ophthalmologist with a three-day history of new floaters and flashes in both eyes. She had a history of primary breast cancer treated by mastectomy and monitored with serial imaging. She underwent right lower lobectomy for a new lung nodule 18 years later. Pathology revealed EGFR positive primary non-small cell lung cancer. Despite treatment, her non-small cell lung cancer recurred and was started on erlotinib 100 mg orally daily. Six weeks later, she developed fevers, fatigue, and diarrhea. Laboratory workup done at this time was negative for infectious etiology and WBC counts remained normal at 6.2 k/microL. She was treated with Tylenol for presumed tumor fever. During this time she developed new flashing lights and floaters, and was referred for further evaluation.

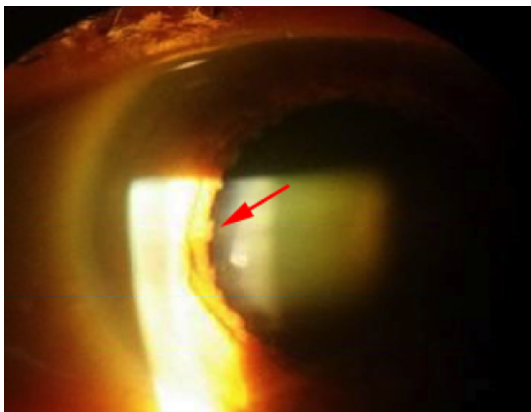


Fig. 1. Slit lamp photograph of the right eye of patient in case 1 demonstrating extensive Koeppel nodules (arrow).

Best-corrected visual acuity was 20/30 in both eyes and intra-ocular pressures were normal. Her anterior segment exam was notable for 2 + cell and 1 + flare in both eyes. Her posterior segment exam was unremarkable.

Antistreptolysin O titer, urine beta-2 microglobulin, ACE, lysozyme, QuantiFERON gold, RPR, FTA-ABS, and a chest X ray were negative and she was diagnosed with bilateral acute simultaneous onset anterior uveitis presumed secondary to erlotinib. She was treated with a topical ophthalmic steroid six times daily and cyclopentolate nightly. Steroids were tapered over four weeks and the inflammation resolved. At one-year follow-up, she remained without inflammation.

Her oncologist discontinued erlotinib the day after presentation to the Uveitis Clinic due to lack of systemic efficacy, and not due to ophthalmic findings.

3. Discussion

The epidermal growth factor receptor (EGFR) signaling pathway plays an important role in regulating cellular processes such as proliferation, survival, and apoptosis.³

EGFR activating mutations occur in about 20% of non-small cell lung cancers (NSCLC), and are associated with progression and poor prognosis.³ Erlotinib is an EGFR inhibitor that has shown significant improvements in response rates and progression-free survival in NSCLC with EGFR mutations when compared to platinum-based chemotherapy.¹

The reported ocular side effects of erlotinib include conjunctivitis, keratoconjunctivitis sicca, and keratitis, and less commonly eyelash trichiasis and trichomegaly, corneal ulceration, and corneal perforation.^{2,4} Although uveitis is not currently listed as an adverse reaction on the manufacturer's website, clinicians should maintain a high level of suspicion in erlotinib-treated patients presenting with ocular complaints. Lim et al. reported a case of a 63-year-old woman with a five day history of decreased vision and eye pain, found to have bilateral anterior uveitis.⁴ She was diagnosed with primary NSCLC and started oral erlotinib 150 mg daily six weeks prior to presentation. After two weeks of treatment with a topical steroid and mydriatic, the uveitis completely resolved. The authors did not specify if erlotinib therapy was discontinued (Lim et al.).⁴ Ali et al. reported a case of a 68-year-old woman who started erlotinib 150 mg PO daily for secondary NSCLC.⁵ At an unspecified time after starting erlotinib, she developed bilateral painful red eyes and fever and was treated by a non-ophthalmologist for presumed conjunctivitis. Erlotinib was stopped and she reported improvement in symptoms. One month later, erlotinib was restarted at a lower dose of 100 mg PO daily and 2 days later the patient developed bilateral anterior uveitis. Erlotinib was discontinued and she was treated with a topical steroid and mydriatic with resolution of uveitis.⁵

In the current small case series, it is not possible to be certain there is a direct causal relationship between erlotinib and bilateral anterior uveitis, although there appears to be an association. In the first case, the uveitis failed to recur despite cessation of topical corticosteroids and continuation of erlotinib. This is in contrast to the previously reported case by Ali et al. in which re-initiation of erlotinib was associated with return of uveitis. This suggests that some people may respond promptly to topical corticosteroid treatment without recurrence of uveitis despite continued use of erlotinib whereas others may require continued topical therapy.

Consideration must be given to alternate etiologies for bilateral, simultaneous-onset anterior uveitis, such as immune recovery uveitis (IRU) and post-infectious autoimmune uveitis. IRU, an immune reconstitution inflammatory syndrome typically described in HIV-infected patients, can manifest as a transient anterior or

posterior uveitis. In the current cases, IRU is unlikely in that the patient has no clinical evidence of immunocompromise throughout treatment. Although CD4⁺ counts are not available at the time of initiation of erlotinib, WBC counts remained normal during the symptomatic time and throughout follow-up. Likewise, post-infectious uveitis resulting from infectious gastrointestinal disease is unlikely given negative workup for fever and diarrhea, including cultures and stool studies in both patients. Diarrhea and fatigue are well known side effects of erlotinib therapy and fevers were presumed to be tumor-related rather than infectious in etiology.

4. Conclusions

We report two additional cases of bilateral acute simultaneous onset, anterior uveitis presumed secondary to erlotinib. In both patients, symptoms started within six weeks after initiation of therapy, along with presumed tumor fever. In the first case, erlotinib was not stopped at any time. The inflammation responded completely to a limited course of topical corticosteroids despite continued use of erlotinib. In the second case, erlotinib was discontinued due to lack of systemic treatment response. These cases highlight a potential association between erlotinib therapy and bilateral, acute, simultaneous-onset anterior uveitis and suggest some patients may respond to topical corticosteroids, despite continued use of the drug.

Patient consent

The study was compliant with the Health Insurance Portability and Accountability Act of 1996 and adhered to the tenets of the Declaration of Helsinki. Verbal consent was obtained to publish

case details including photographs, which has been documented in writing.

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