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Publication Date

2024-06-01

DOI

10.1016/j.ajoc.2024.102063

Peer reviewed

American Journal of Ophthalmology Case Reports 34 (2024) 102063

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Bilateral optic neuropathy associated with lorlatinib monotherapy for ALK-positive metastatic lung adenocarcinoma

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ARTICLE INFO

Keywords:
Lorlatinib associated optic neuropathy
Lorlatinib associated vision loss
Toxic optic neuropathy
ALK/ROS1 inhibitor
ALK-Positive adenocarcinoma
Non-small cell lung cancer

ABSTRACT

Purpose: This report details the characteristics of a case of bilateral optic neuropathy during treatment with oral lorlatinib for ALK-positive metastatic adenocarcinoma of the lung.

Observations: A 57-year-old woman with metastatic adenocarcinoma of the lung receiving treatment with lorlatinib presented to the ophthalmology urgent care with bilateral loss of vision that had progressed to no light perception over the previous 2 weeks. She was hospitalized for an extensive autoimmune, infectious, neoplastic, and paraneoplastic workup, which revealed enhancement of both optic nerves extending up to the optic chiasm and an area of restricted diffusion in the splenium of the corpus callosum on MRI. Lorlatinib was discontinued by her oncologist and she received treatment with five days of pulse-dose intravenous solumedrol as well as five days of plasmapheresis with gradual improvement in her vision. In follow-up, her vision had improved to 20/40 and 20/30.

Conclusion and importance: There have been few reports describing vision loss associated with lorlatinib, an ALK/ROS1 targeted tyrosine kinase inhibitor used to treat metastatic lung adenocarcinoma. This report details the characteristics of a case of bilateral retrobulbar optic neuropathy as well as the treatment and recovery of such a case. Further exploration is needed in order to improve our understanding of the pathogenesis of this rare but potentially devastating adverse effect.

1. Introduction

Lorlatinib is a third-generation inhibitor of anaplastic lymphoma kinase (ALK) and c-ROS oncogene-1 (ROS1), approved for treating ALK-positive adenocarcinoma of the lung.[1,2] The ALK inhibitor class of medications are a class of tyrosine kinase inhibitors with reported side effects of visual disturbances, defined by a wide range of symptoms including dry eyes, photopsia, presbyopia, and floaters.[3,4] Lorlatinib, however, has been shown to cause fewer visual disturbances than first generation ALK inhibitor crizotinib, and had no reported grade three or four visual adverse events in an early clinical trial.[1] Crizotinib did have one reported grade three or four visual adverse event,[5] and one case study has described optic neuropathy following crizotinib use.[6] Post-marketing safety analyses showed that the primary reported side effect of lorlatinib was related to metabolism and nutrition disorders,[7] and an interim analysis on the efficacy of lorlatinib showed that the majority of grade three or four adverse events from lorlatinib use was related to altered lipid concentrations while no visual disturbances were reported in this analysis.[8] Thus, despite visual disturbances being a known side effect of the medication, there are few published cases describing lorlatinib ocular toxicity in detail. One case series demonstrated two patients with vision loss consistent with optic neuropathy within two to three months of initiating lorlatinib,[9] but this report documents that optic neuropathy was determined based on the clinical exam findings and describes little detail regarding the full medical work up. Here we present a case of optic neuropathy due to lorlatinib use and subsequent treatment.

2. Case report

A 57-year-old woman with a history of ALK positive adenocarcinoma of the lung that was complicated by metastases to the spine, status post T3-5 laminectomy and external beam radiation, without prior chemotherapy was treated with oral lorlatinib 100 mg once daily. Two months after starting the medication, during a follow up visit she reported four days of severe vision loss in both eyes. Lorlatinib was discontinued and

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https://doi.org/10.1016/j.ajoc.2024.102063
Received 16 February 2024; Received in revised form 29 March 2024; Accepted 9 April 2024
Available online 25 April 2024

an expedited MRI of the brain and orbits was ordered. She was referred to ophthalmology for further evaluation. The patient presented to the ophthalmology urgent care clinic six days later. At this visit, she reported two weeks of painless, progressive vision loss, sharing that her vision had been completely dark for the last three days. She denied pain with eye movements. Exam demonstrated no light perception vision in both eyes, large minimally reactive pupils bilaterally with left relative afferent pupillary defect (RAPD). Dilated fundus exam revealed trace disc edema, more prominent on the left, with mildly dilated venules. MRI orbits (Fig. 1A–C) demonstrated bilateral T1 enhancement and increased T2 signal of the whole length of the optic nerve up to the chiasm, more pronounced on the left than right. MRI brain (Fig. 1D) revealed a small curvilinear focus of restricted diffusion and FLAIR (Fig. 1D) hyperintensity in the splenium of the corpus callosum and was otherwise normal. Given these findings, the patient was admitted for expedited work up and treatment.

Work-up included lumbar puncture, additional imaging, and serological blood tests to rule out infectious or infiltrative process, including leptomeningeal carcinomatosis. Initial studies were grossly unremarkable, and after cerebrospinal fluid (CSF) samples were sent for cell count, protein, glucose, culture, and cytology, treatment was started with 1 g intravenous (IV) methylprednisolone per day for five days.

One day after starting IV steroids, the patient's vision began to improve. At the end of her five-day course of steroids, her visual acuity was counting fingers at about four feet in the right eye and counting fingers at about two feet in the left eye. Subsequently, plasmapheresis was initiated, and she received daily exchanges for five days. After completion of the plasmapheresis, her corrected near visual acuity was 20/800 on a near card in the right eye and counting fingers at three feet in the left eye. The patient was discharged on oral prednisone at 1 mg per kilogram per day with instructions to taper by 10 mg per day each week.

The work-up was largely unremarkable. CSF cytology was normal with negative oligoclonal bands. Rheumatoid factor was mildly elevated at 26 IU/mL (reference <14 IU/mL), but additional autoimmune serology was normal, including thyroid stimulating hormone, double stranded deoxyribonucleic acid antibody, Smith antibody, ribonucleoprotein antibody, anti-Sjögren's-syndrome-related A and B antibodies, cardiolipin antibodies, antineutrophilic cytoplasmic antibodies (ANCA), myeloperoxidase antibody, proteinase-3 antibody. Paraneoplastic autoantibody and encephalopathy panel revealed voltage gated potassium channel (VGKC) complex antibody positivity at 0.13 nmol/L, but was otherwise unremarkable, including negativity for collapsin response-mediator protein (CRMP) 5, N-methyl-D-aspartate (NMDA), Purkinje cell cytoplasmic antibody (PCA) 1 & 2, septin, contactin-associate protein-like (Caspr) 2, amphiphysin ab, anti-glial nuclear antibody (AGNA) 1, anti-neuronal nuclear antibody (ANNA) 1–3. Demyelinating disease antibodies including neuromyelitis optica (NMO)/aquaporin (AQP) 4 and myelin oligodendrocyte glycoprotein (MOG) were negative. Infectious work up for the hepatitis viruses, syphilis, tuberculosis, human T-lymphotropic virus (HTLV) I/II, and bartonella was negative. MRI of the cervical, thoracic, and lumbar spine did not demonstrate any evidence of demyelinating lesions or increased metastatic burden.

Following up in the neuro-ophthalmology clinic four weeks after discharge, best corrected visual acuity (BCVA) was 20/40 in the right

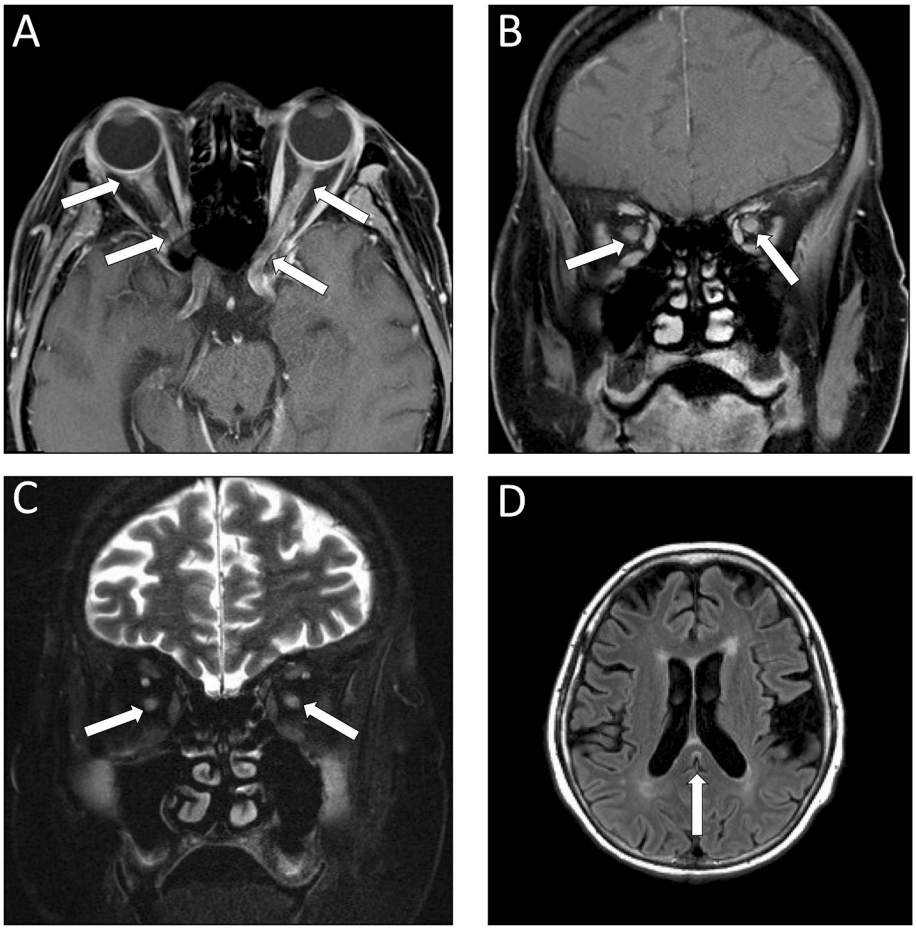

Fig. 1. Magnetic resonance imaging (MRI) of the orbits and brain with and without contrast and fat suppression. T1-weighted post contrast axial (A) and coronal (B) cuts show bilateral optic nerve enhancement. T2-weighted coronal (C) cut demonstrates increased signal which can be seen along the whole nerve. T2-weighted FLAIR axial (D) cut demonstrates a curvilinear focus of hyperintensity in the splenium of the corpus callosum consistent with cytotoxicity.

eye and 20/30 in the left eye. Color vision remained diminished with only the control plate seen on Ishihara pseudoisochromatic testing in each eye. Humphrey visual field (Carl Zeiss Meditec, Inc. Dublin, CA) 30-2 testing demonstrated bilateral central scotomas (Fig. 2), and optical coherence tomography (Carl Zeiss Meditec, Inc. Dublin, CA) imaging showed diffuse thinning of the ganglion cell layer and the inner plexiform layer (Fig. 3). Her retinal nerve fiber layer thickness remained full, and her optic nerve did not develop pallor on subsequent visits. For cancer treatment, the patient's oncologist initiated infusions of carboplatin, pemetrexed, and pembrolizumab every 3 weeks. The patient's medical condition unfortunately continued to worsen, and she transitioned her care to palliative care.

3. Discussion

We describe a patient who experienced severe bilateral optic neuropathy while receiving lorlatinib monotherapy for treatment of ALK positive adenocarcinoma of the lung. The patient initially presented with a painless, rapid, severe decline in vision, and enhancement of both optic nerves on MRI, therefore a broad differential was considered. Given her history of metastases to the spine, there was also a concern of leptomeningeal carcinomatosis, but there was no leptomeningeal enhancement on MRI and her CSF studies did not support this. Paraneoplastic syndromes were considered, but only the VGKC antibody was positive. This antibody has never been associated with optic neuropathy, and it is very unlikely that this finding provides significant insight to the etiology of our patient's condition. Neuroimaging ruled out compressive or infiltrative optic neuropathy. Furthermore, the presence of a cytotoxic lesion in the corpus collosum, which was hyperintense on FLAIR and restricted on diffusion weighted imaging supports neurotoxicity (Fig. 1D).

Given the timing of the patient's vision loss within two months of starting lorlatinib followed by improvement after discontinuation and treatment with steroids and plasmapheresis, as well as no evidence of demyelinating disease in spine nor brain, we feel that lorlatinib toxicity should be considered as a causative factor for her vision loss. Collaboration by multiple specialties, including oncology, rheumatology, neurology, and ophthalmology contributed to this conclusion in our patient's case.

Loratinib is known to be highly effective in preventing CNS progression in patients with ALK positive non-small cell lung cancer.[10] Moreover, recent interim analysis of the phase three study showed that lorlatinib had superior progression-free survival and time to intracranial progression in patients with and without brain metastases.[8] Lorlatinib inhibits ALK and ROS1 which leads to cell cycle arrest at G1/S-phase, resulting in cell apoptosis. The medication has 100 % enteral bioavailability, and its 0.75 serum/CSF concentration ratio makes it an excellent treatment option in patients with metastases to the central nervous system.[2] Visual disturbances are a known side effect of ALK inhibitors, but several studies have shown that lorlatinib has a less severe visual side effect profile than first generation ALK inhibitor crizotinib,[1,2] which has been reported in association with optic neuropathy.[6] A study assessing the ERGs of rats being treated with crizotinib and PF-06463922 (lorlatinib) demonstrated decreased b-wave amplitude in the critozinib-treated group while no changes were seen in the lorlatinib-treated group.[11] In a meta-analysis and a separate post marketing safety analysis of ALK inhibitor associated adverse effects, visual changes were reported almost exclusively with crizotinib use.[7,12] Lorlatinib was associated with hypercholesterolemia metabolism disorders, while other ALK inhibitors such as alectinib and brigatinib were associated with hepatobiliary disorders and respiratory disorders, respectively.[7] Nevertheless, a case reports on two patients with lorlatinib-related vision changes similarly described patients that experienced vision changes within two months of initiating lorlatinib, similar to the time course of the patient in this case.[8] In both cases, the diagnosis of lorlatinib toxicity was a clinical one, and only for one patient was an MRI performed to assess for further apparent pathology. In our case, we demonstrate and highlight the complete work up which not only revealed enhancement of the optic nerves, but also the negative infectious, autoimmune, neoplastic, and paraneoplastic work up, which

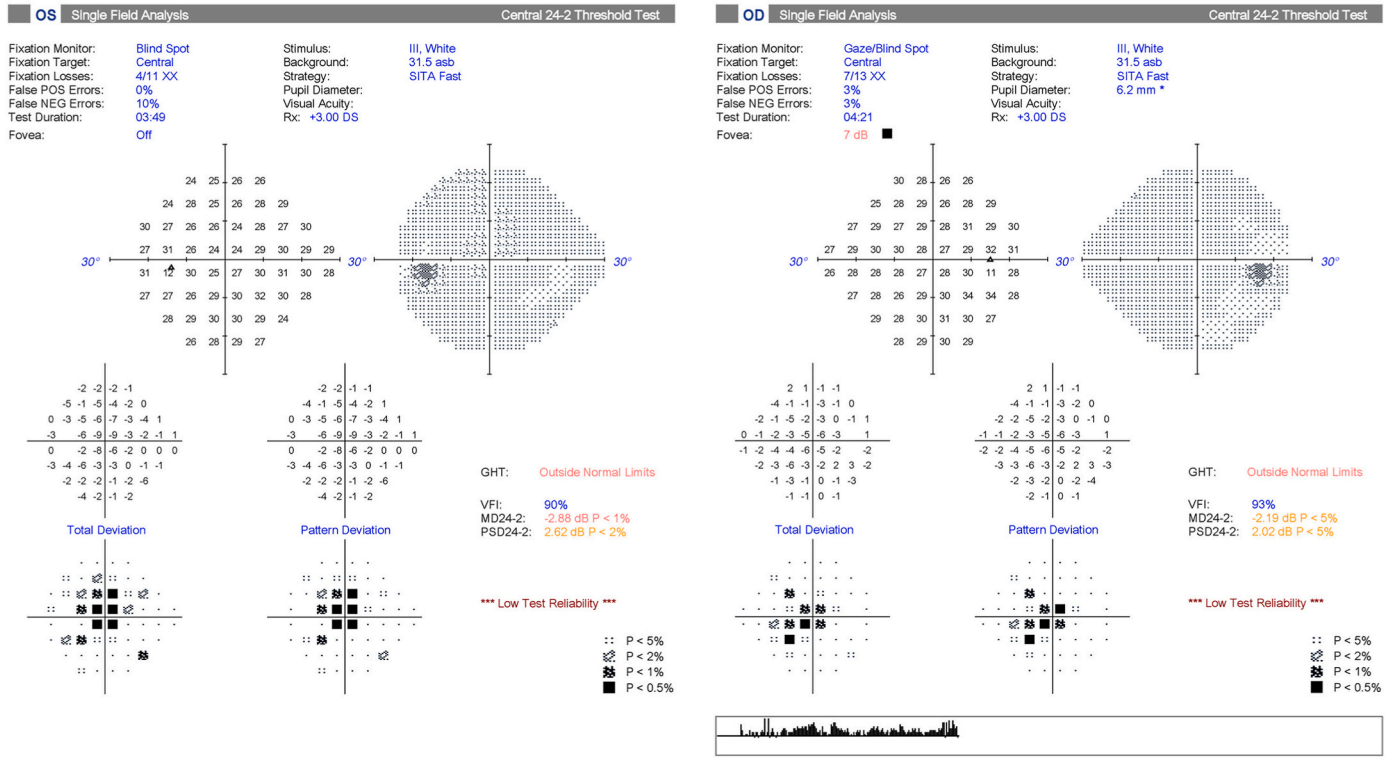

Fig. 2. Humphrey visual field 30-2 testing demonstrated bilateral central scotomas.

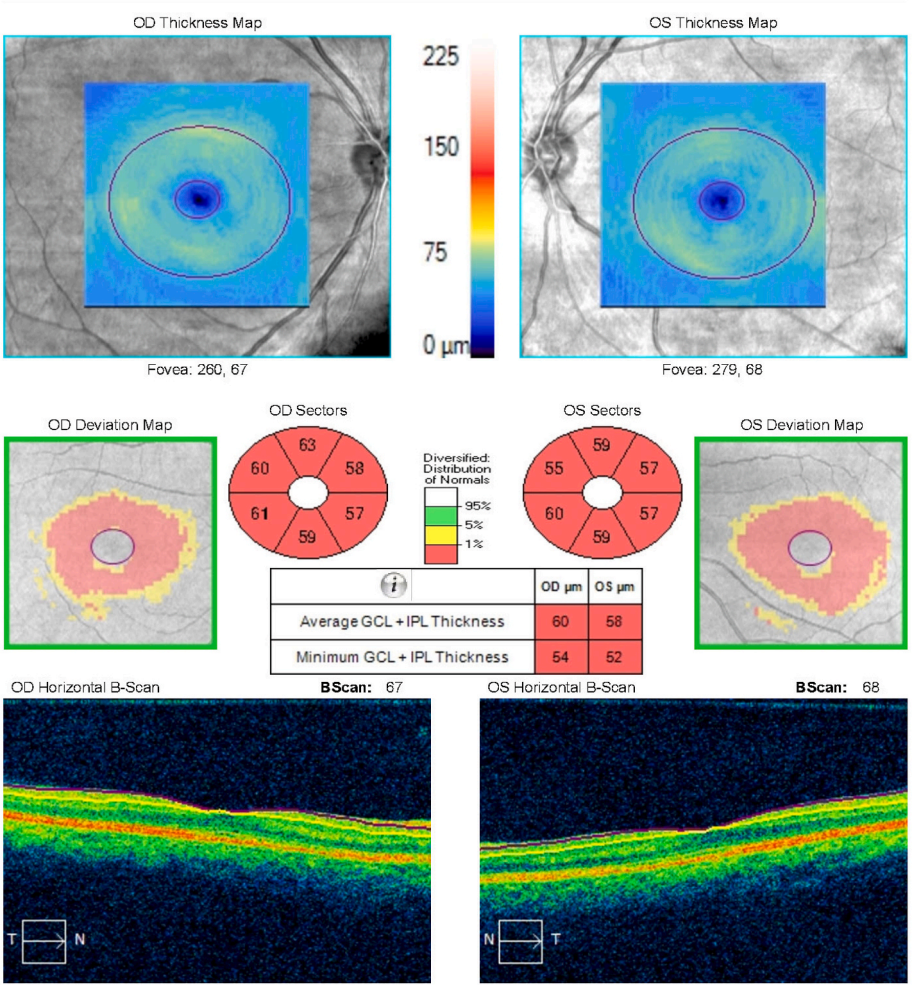

Fig. 3. Optical coherence tomography demonstrates severe bilateral ganglion cell layer and inner plexiform layer thinning.

should be performed in such patients.

The true etiology of lorlatinib-associated optic neuropathy remains unclear at this time, and the condition requires further study in order to better characterize the history of such cases and aid our understanding of the underlying process, whether the monoclonal antibody has a direct toxic effect on the optic nerves, a hypersensitivity reaction occurs, or there is some combination of the two. Given that there are no specific or confirmatory tests available, this condition is a diagnosis of exclusion. A complete eye exam and a work-up for alternative causes of painless vision loss in a cancer patient, such as metastatic disease, stroke, or infectious process should be performed in any event of symptom recurrence. Our patient's vision loss continued to progress for about 3 days following cessation of lorlatinib, which has a plasma half-life of 23.9 ± 4.9 hours and an expected time to clearance around 4 days. While our patient's nadir in visual acuity reportedly occurred 3 days following drug cessation, her vision remained at no light perception and did not begin to improve until after she received treatment with high dose IV steroids. Her visual recovery was then slow but significant. Our patient's vision improved with high dose IV steroid treatment, as did the cases presented by Karakaya et al.[9] Our patient demonstrated further improvement with plasmapheresis, suggesting that there may be an additive effect of steroids and plasmapheresis for reversing lorlatinib toxicity. Additional treatment options to consider for these patients may include intravenous immunoglobulin (IVIg) therapy and even observation in fragile patients with poor overall prognosis. Steroid sparing immunomodulatory therapies might be considered if patients require long-term immunosuppression. Furthermore, after stopping lorlatinib, consideration to switching to other alternative chemotherapy agents should be made in discussion with the oncology team to ensure that there is minimal disruption to the ongoing cancer treatment. In this case, the patient was switched to pembrolizumab, which is a programmed cell death protein 1 (PD-1) inhibitor, although other possibilities to consider include alternative ALK inhibitors such as alectinib or brigatinib.

4. Conclusion

Severe painless vision loss may be considered a rare, but possible adverse effect of lorlatinib, and early detection of ocular toxicity with cessation of the medication is imperative. Furthermore, the condition warrants a proper work-up and treatment with high dose intravenous steroids and plasmapheresis may allow for significant recovery of sight.

Patient consent

Verbal consent was obtained by the patient and written consent was obtained from their family.

Financial disclosures

None to report.

Funding

No funding or grant support.

Authorships

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

CRediT authorship contribution statement

Alan W. Kong: Writing – review & editing, Writing – original draft, Conceptualization. **Alexander R. Engelmann:** Writing – review & editing, Writing – original draft, Conceptualization. **Mahdieh Hosseini:** Writing – review & editing, Writing – original draft. **Laura Bonelli:** Writing – review & editing, Writing – original draft, Supervision, 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.

Acknowledgements

None.

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