Received: 12 January 2023 | Accepted: 25 January 2023

DOI: 10.1111/1759-7714.14818

CASE REPORT

WILEY

Iris metastasis as resistance mechanism to atezolizumab, carboplatin, and etoposide but responds to additional irinotecan and anlotinib in a small cell lung cancer patient

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Abstract

Small cell lung cancer (SCLC) is an aggressive malignancy associated with poor prognosis. Metastasis to sites outside the chest at the time of initial diagnosis, such as bone, brain, and liver metastasis have been found in most SCLC patients. Iris metastases from SCLC have rarely been previously reported, and often cause eye pain and blindness in patients. Here, we report a patient with SCLC who presented with iris metastasis in the right eye and metastasis in the left adrenal gland due to disease progression on first-line therapy, which subsequently caused pain and blindness in the right eye. The patient was treated with second-line irinotecan combined with anlotinib and atezolizumab and did not receive any local treatment in the right eye. After only one cycle of treatment, the iris metastases in the right eye were smaller than before, and the visual acuity in the right eye recovered. At the same time, her left adrenal metastases were also significantly smaller than before. Our case suggests that systemic therapy with effective treatment options can similarly improve iris metastases in patients.

KEYWORDS

immunotherapy, iris metastases, small cell lung cancer

INTRODUCTION

Small cell lung cancer (SCLC) is a tumor with high invasiveness and poor prognosis.

Although small cell lung cancer is sensitive to chemotherapy or radiotherapy in the early stage, resistance soon develops and tends to recur after discontinuation of the drug.

Distant metastases of SCLC are a common clinical concern. At the time of diagnosis, about 70% of SCLC patients have already developed metastatic disease, with macrometastases most typically found in the lymph nodes, brain, liver, and bones.[1]

Here, we describe a patient with SCLC in whom the symptoms caused by iris metastasis were the only signs after resistance after multimodality treatment.

CASE REPORT

A 57-year-old woman was diagnosed with SCLC (cT4N2M0) on February 23, 2021 by computed tomography (CT)-guided lung biopsy. Immunohistochemistry showed CD45-, CK5/6-, TTF-1+, CD56+, Syn+, napsinA-, CgA (Focally positive), P40-, CK7-, Ki-67 (uo to 60%, Figure 1a). She had received four cycles of carboplatin/etoposide in combination with atezolizumab and two cycles of atezolizumab maintenance therapy. The primary lung tumors had shrunk significantly after two cycles of treatment and the imaging evaluation was partial response (PR) disease (Figure 1b,c). The patient then had several radiological examinations which assessed the treatment as sustained PR.

The patient visited her ophthalmologist because of pain and blindness in the right eye on December 10, 2021.

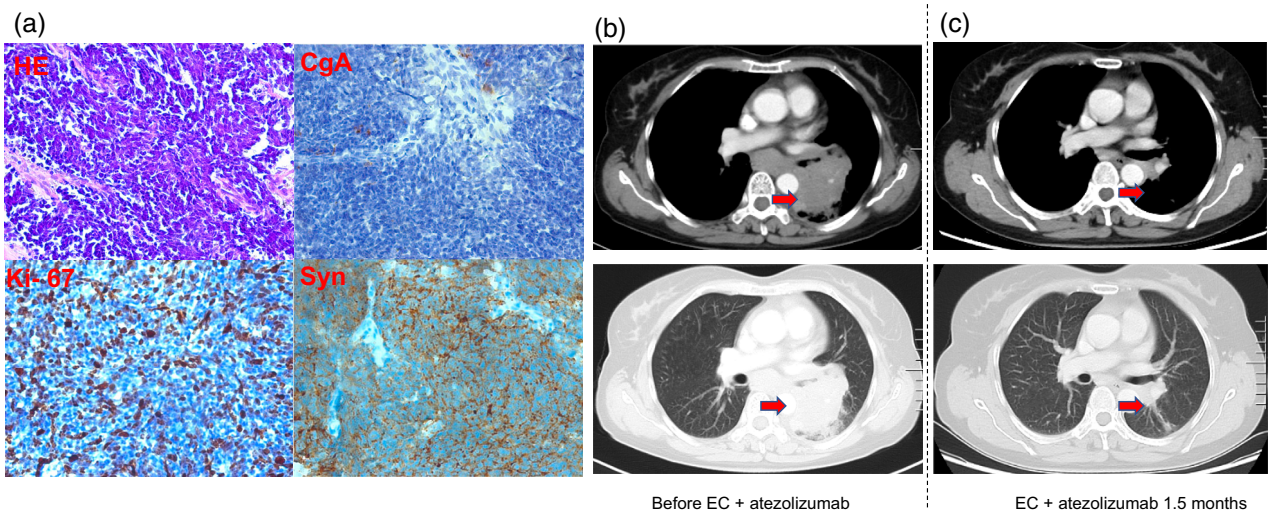

FIGURE 1 (a) Photograph of small cell lung cancer. (b) Radiological image of baseline. (c) Radiological image of best response for carboplatin and etoposide in combination with atezolizumab

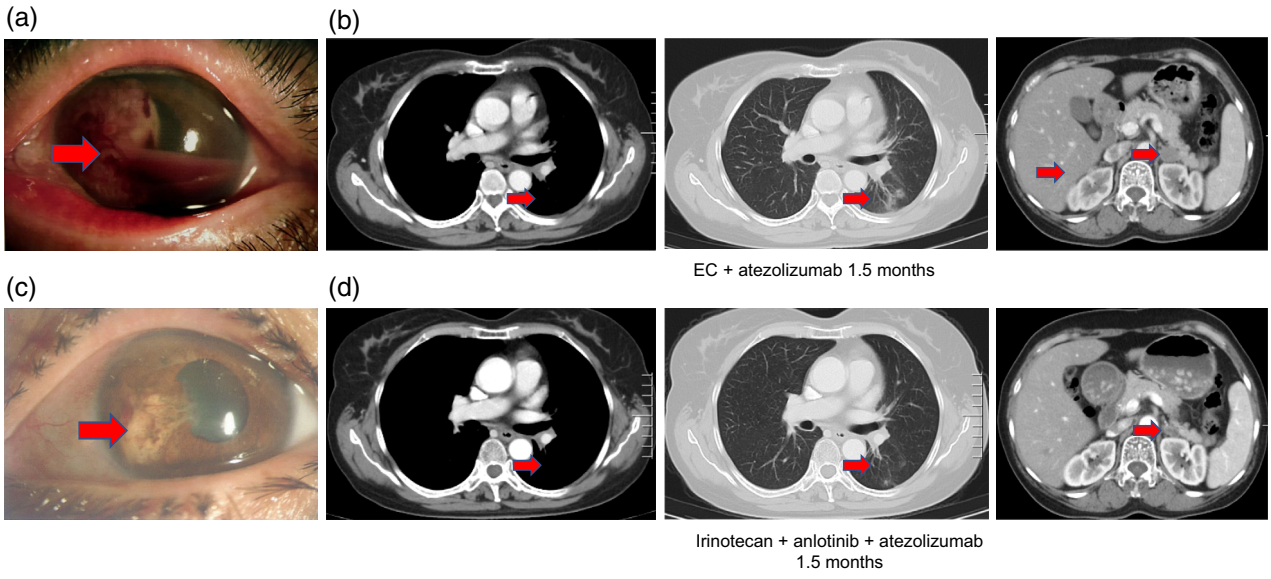

FIGURE 2 (a) Iris metastasis in the right eye prior to systemic therapy. (b) Radiological image of progression for carboplatin and etoposide in combination with atezolizumab. (c) Iris metastasis in the right eye after one cycle of irinotecan combined with atezolizumab plus anlotinib. (d) Radiological image after 1.5 months of irinotecan combined with atezolizumab plus anlotinib

Examination showed a positive relative afferent pupillary defect (RAPD) in right eye. Slit lamp biomicroscopy revealed conjunctival hyperemia and a large temporal gray irregular iris mass, which was associated with peripheral anterior synechiae (PAS) of the iris and iris neovascularization (Figure 2a). The patient came to our hospital with CT images suggestive of left adrenal metastases (Figure 2b). These results suggested disease progression. The patient was then treated with one cycle of irinotecan combined with atezolizumab plus anlotinib and did not receive any local treatment in her right eye. Visual acuity recovered with significant pain relief of the right eye. Examination revealed that the iris metastasis of the right eye had markedly decreased (Figure 2c). The CT image after two cycles of treatment showed that metastases in the left adrenal gland had also decreased (Figure 2d).

DISCUSSION

Metastasis occurring in the iris is quite a rare complication.[2–4] Iris metastasis generally originates from primary tumors in the breast and lung cancer.[5] In a previous study, approximately 30% of patients had no diagnosis of

primary tumor location at the time ocular metastasis was discovered.[6] A total of 22% iris metastases were found before and 33% after systemic metastases in another study.[2] The most common complaints are blurred vision and pain. Clinical features include iris mass, neovascularization, and corneal precipitates.[2,5]

Treatment of iris metastases includes systemic chemotherapy, external beam radiotherapy, plaque radiotherapy, surgical excision, enucleation, or observation. In a previous case analysis, it was found that the occurrence of iris metastasis may be related to neovascularization.[2] Some patients were also treated with intravitreal injection of bevacizumab and a good outcome was achieved. The eye is also an immunological privileged organ that suppresses inflammation induced by "anterior chamber-associated immune deviation" (ACAID). Immunological responses to antigens from the eye are significantly attenuated.[7] Only a few studies of immune checkpoint inhibitors (ICIs) treatment for ocular metastases have been published, indicating that evidence of immunotherapy for ocular metastases is limited and deserves further exploration.[8]

Iris metastases are often associated with neovascularization, and antineovascularization is often used to treat iris metastases.[2] For this patient, we used anlotinib for antineovascularization. Anlotinib is a new orally administered tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptors (PDGFR) and c-kit. A randomized, double-blind, placebo-controlled Phase 2 study was conducted in 120 Chinese patients with advanced SCLC (ALTER 1202 study), and median progression-free survival (PFS) was 4.3 months in the anlotinib arm and 0.7 months in the placebo arm (HR, 0.19; $p < 0.0001$). In addition, anlotinib prolonged overall survival time (OS) (7.3 vs. 4.9 months). Therefore, anlotinib was approved by cFDA in 2019 as the standard third-line treatment for patients with ES-SCLC.[9] Bevacizumab is a humanized monoclonal antibody targeting VEGF and is widely used in the treatment of non-small cell lung cancer, intestinal cancer, etc. In two randomized studies of first-line treatment of extensive-stage small cell lung cancer, bevacizumab combined with etoposide and cisplatin resulted in an improvement in PFS, but OS was not prolonged.[10,11] There have been few studies on the use of ramucirumab. However, a phase 1b study of ramucirumab in combination with irinotecan plus cisplatin in chemo-naïve patients with extensive-stage small cell lung cancer showed the satisfactory tolerability and efficacy of ramucirumab at 10 mg/kg in combination with irinotecan plus cisplatin in chemo-naïve patients with extensive-stage SCLC.[12] However, ramucirumab is currently unavailable in China. Other antiangiogenic drugs including endostar, sunitinib, sorafenib, vandetanib, cediranib, and nintedanib or ziv-aflibercept, have not achieved satisfactory results.[9,13]

Antineovascularization therapies are also often used in the treatment of other ocular diseases. Many disease states involving the eye, such as diabetic retinopathy, retinal vein occlusion, age-related macular degeneration (AMD), and retinopathy of prematurity (ROP), are associated with VEGF signaling. Ocular anti-VEGF therapy is very effective in treating people who have these eye diseases.[14,15] Intravitreal bevacizumab has been reported to be used for iris neovascularization and neovascular glaucoma secondary to ischemic retinal disease.[16] In previous studies, anlotinib has been reported to inhibit pathological ocular neovascularization.[17]

In our report, we experienced a rare case. This patient was considered resistant to first-line therapy; thus, irinotecan was used as the second-line chemotherapeutic agent in combination with atezolizumab, which was well-tolerated in prior line therapy, and the antiangiogenic therapy of anlotinib was also added to the combination. The iris metastasis rapidly reduced in size after only one cycle of the combination therapy, suggesting that iris metastasis may benefit from combination treatments.

AUTHOR CONTRIBUTIONS

Yongchang Zhang: Conceptualization, organization, data collection, auditing, supervision, project administration, funding acquisition, writing- reviewing and editing.

Zhe Huang: Data curation, methodology, formal analysis, writing-original draft preparation, writing- reviewing and editing.

Yongchang Zhang and Zhe Huang: Formal analysis, writing- reviewing and editing.

All authors approved the final version of the manuscript.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

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REFERENCES

1. Ko J, Winslow MM, Sage J. Mechanisms of small cell lung cancer metastasis. EMBO Mol Med. 2021;13:e13122.
2. Liu T, Bai F, Yang L, Liu L, Xiao J, Liu X. Primary tumour type, clinical features, treatment and outcome of patients with iris metastasis. Ocul Immunol Inflamm. 2022;30:1726–32.
3. Shields CL, Shields JA, Gross NE, Schwartz GP, Lally SE. Survey of 520 eyes with uveal metastases. Ophthalmology. 1997;104:1265–76.
4. Shields JA, Shields CL, Kiratli H, et al. Metastatic tumors to the iris in 40 patients. Am J Ophthalmol. 1995;119:422–30.
5. Shields CL, Kaliki S, Crabtree GS, Peshtani A, Morton S, Anand RA, et al. Iris metastasis from systemic cancer in 104 patients: the 2014 Jerry A Shields Lecture. Cornea. 2015;34:42–8.
6. De Potter P. Ocular manifestations of cancer. Curr Opin Ophthalmol. 1998;9:100–4.
7. Streilein JW. Ocular immune privilege: the eye takes a dim but practical view of immunity and inflammation. J Leukoc Biol. 2003;74:179–85.
8. Fernandez-Diaz AB, Garcia-Medina A, Ferrer-Guillen B, et al. Eye immune privilege? Nivolumab plus ipilimumab: successful treatment in a patient with cutaneous melanoma and ocular metastases. Melanoma Res. 2019;29:345–7.

9. Shi J, Cheng Y, Wang Q, Li K, Wu L, Han B, et al. Anlotinib as third- or further-line therapy for short-term relapsed small-cell lung cancer: subgroup analysis of a randomized phase 2 study (ALTER1202). Front Med. 2022;16:766–72.
10. Spigel DR, Townley PM, Waterhouse DM, Fang L, Adiguzel I, Huang JE, et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. J Clin Oncol. 2011;29:2215–22.
11. Pujol JL, Lavole A, Quoix E, Molinier O, Souquet PJ, Barlesi F, et al. Randomized phase II-III study of bevacizumab in combination with chemotherapy in previously untreated extensive small-cell lung cancer: results from the IFCT-0802 trialdagger. Ann Oncol. 2015;26:908–14.
12. Kenmotsu H, Mori K, Mizuno R, Mamesaya N, Kobayashi H, Omori S, et al. Phase 1b study of ramucirumab in combination with irinotecan plus cisplatin in chemo-naive patients with extensive-stage small-cell lung cancer. Lung Cancer. 2022;164:39–45.
13. Montanino A, Manzo A, Carillio G, Palumbo G, Esposito G, Sforza V, et al. Angiogenesis inhibitors in small cell lung cancer. Front Oncol. 2021;11:655316.
14. Sene A, Chin-Yee D, Apte RS. Seeing through VEGF: innate and adaptive immunity in pathological angiogenesis in the eye. Trends Mol Med. 2015;21:43–51.
15. Uemura A, Fruttiger M, D'Amore PA, de Falco S, Joussen AM, Sennlaub F, et al. VEGFR1 signaling in retinal angiogenesis and microinflammation. Prog Retin Eye Res. 2021;84:100954.
16. Wakabayashi T, Oshima Y, Sakaguchi H, et al. Intravitreal bevacizumab to treat iris neovascularization and neovascular glaucoma secondary to ischemic retinal diseases in 41 consecutive cases. Ophthalmology. 2008;115:1571–80.
17. Lu C, Zhang Q, Zhang H, Li X, Jiang Q, Yao J. A small molecular multi-targeting tyrosine kinase inhibitor, anlotinib, inhibits pathological ocular neovascularization. Biomed Pharmacother. 2021;138:111493.

How to cite this article: Huang Z, Zhang Y. Iris metastasis as resistance mechanism to atezolizumab, carboplatin, and etoposide but responds to additional irinotecan and anlotinib in a small cell lung cancer patient. Thorac Cancer. 2023;14(8):779–82. https://doi.org/10.1111/1759-7714.14818