

# Development of a new choroidal metastasis in resistance to crizotinib therapy in anaplastic lymphoma kinase-rearranged non-small cell lung cancer

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## INTRODUCTION

Non-small cell lung cancer (NSCLC) is a common malignant disease with an extremely poor prognosis<sup>[1]</sup>. Lung cancer has been reported to metastasize to the eye in 0.2% to 7% of patients based on clinical studies, and in 6% to 7% of patients based on postmortem histopathologic studies<sup>[2]</sup>. The choroid is the most common ocular tissue affected by metastatic disease. Choroidal metastasis represents the most common form of intraocular malignancies<sup>[3]</sup>. Presence of choroidal metastasis is indicative of widespread dissemination of the initial neoplasm, and is usually accompanied by a poor prognosis<sup>[4]</sup>.

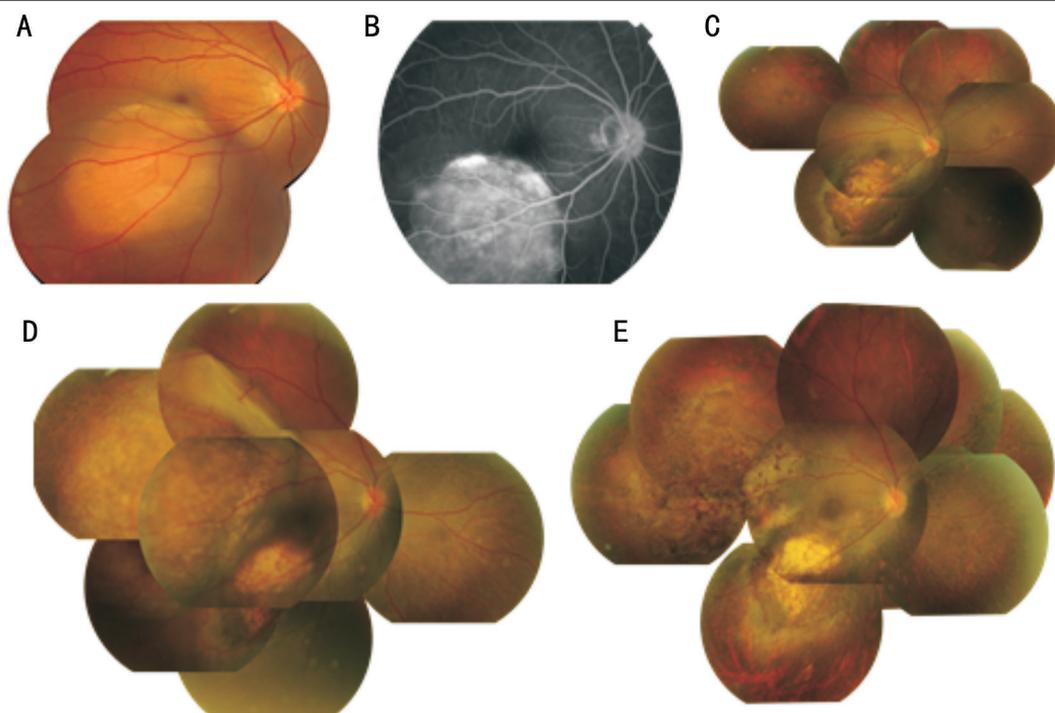
Advances at the molecular level have enabled finer categorization into distinct subsets of NSCLC. Molecular targeted therapy have shown improved clinical outcomes<sup>[5]</sup>. Several reports showed significant shrinkage of choroidal metastases and a prolonged progression-free survival (PFS)<sup>[6-9]</sup>.

Here, we present a case of anaplastic lymphoma kinase (ALK)-rearranged NSCLC with symptomatic ocular metastasis at the time of diagnosis, which completely regressed to a flat scar with crizotinib therapy. However, at 16mo of treatment, a new choroid metastasis was revealed, which was treated and regressed with the second generation of anti-ALK agents.

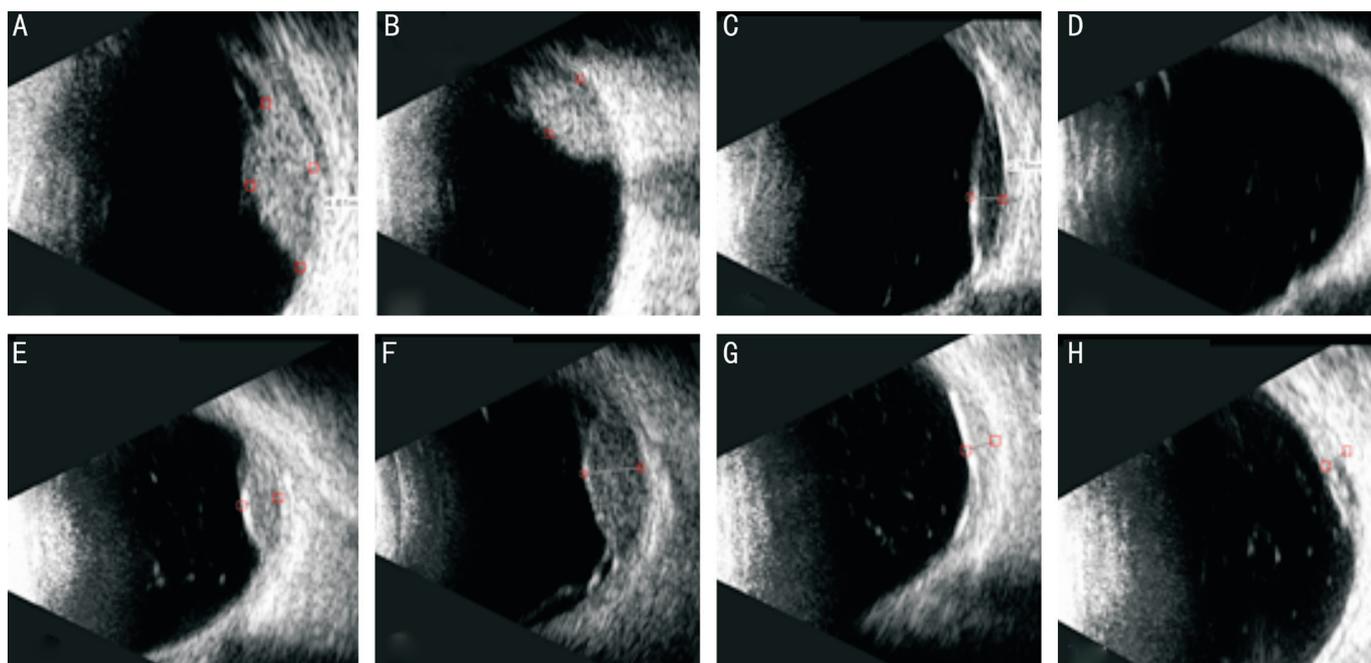
## CASE PRESENTATION

A 35-year-old Chinese female, non-smoker, presented with a complaint of blurred vision in her right eye lasting 3d. The patient provided written informed consent for this case report. Dilated funduscopy examination revealed an amelanotic choroidal mass near the macula of the right eye, inferior temporal to the optic nerve (Figure 1A). Fluoroangiography revealed non-primitive choroidal retinal neoplasm (Figure 1B). Ultrasonographic examination showed a dome-shaped lesion with high internal reflectivity (Figure 2A). The patient recalled having a headache on the right side of the head 2wk ago. A magnetic resonance imaging (MRI) scan of the head detected an intraocular lesion with no intracranial lesion (Figure 3A). Thorax and abdomen CT-scan was performed and revealed a nodule in the left upper lung (Figure 4A). The right supraclavicular lymph node biopsy confirmed an adenocarcinoma (Figure 5). Genotype testing yielded negative for epidermal growth factor receptor (EGFR) mutation, but positive for ALK translocation. The PET/CT scan revealed positive signals in No. 6 and No. 7 ribs on the right side, and the acetabulum on the left side (Figure 6A). Clinical TNM staging at the time of diagnosis was T1aN3M1.

After two courses of chemotherapy with cisplatin, the patient complained of worsening vision. The funduscopy showed an enlarged mass and the ultrasonographic examination showed an increase in the height of the mass (Figure 2B). The treatment was switched to crizotinib, 250 mg orally twice daily. After two weeks of crizotinib therapy, the right eye's vision improved from 20/200 to 20/50. The choroid lesion regressed and the height of the mass was reduced (Figure 2C). On the 4<sup>th</sup> month of crizotinib therapy, the ultrasonographic photograph showed the mass completely flattened (Figure 2D). Vision remained stable at 20/50. The funduscopy examination showed an atrophic scar at the initial lesion site, surrounded by diffused depigmentation and punctual pigmentation (Figure 1C). The thorax CT revealed regression of the primary lesion (Figure 4B). The condition remained stable until the 16<sup>th</sup> month of crizotinib therapy, when a new metastasis was detected by both ultrasonographic (Figure 2E) and fundoscopic (Figure 1D) examination. The new metastasis was superior temporal to the initial one. The crizotinib therapy continued for 2 more weeks because



**Figure 1 Fundus photographs** A: Right fundus image revealed a large dome-shaped amelanotic tumor; B: Fluoroangiography revealed non-primitive choroidal retinal neoplasm; C: The choroid lesion regressed to a flattened scar after 4mo of crizotinib therapy; D: New metastasis appeared on the superior temporal side of the initial lesion on the 16mo of treatment; E: Regression of the new metastasis 2wk after AP26113 therapy.



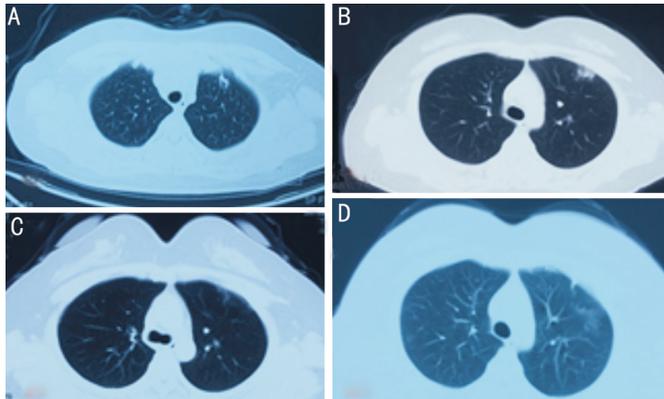
**Figure 2 Ultrasound B scan** A: Ultrasound B revealed the initial dome-like choroid lesion with the height 4.61 mm; B: One month later, after two courses of chemotherapy, the height of the lesion increased to 5.29 mm; C: The height of the lesion reduced to 2.75 mm two weeks after crizotinib therapy; D: The lesion regressed to a flat scar on the 4<sup>th</sup> week of crizotinib therapy; E: A new metastasis revealed with the height 3.34 mm on the 16<sup>th</sup> month of therapy; F: The height of new metastasis increased to 5.14 mm after 2 more weeks with crizotinib therapy; G: The height of new metastasis reduced to 2.48 mm after one week of AP26113 therapy; H: The height of the mass reduced to 1.91 mm after three weeks of AP26113 therapy.

the thorax CT (Figure 4C) and PET-CT (Figure 6B) did not find any progression of the malignancy. However, the patient later presented with red eye, decreased vision to 20/200, ocular edema and pain. The fundus photography showed the progression of the new metastasis. The ultrasonographic examination revealed an increase in the height of the mass (Figure 2F). The

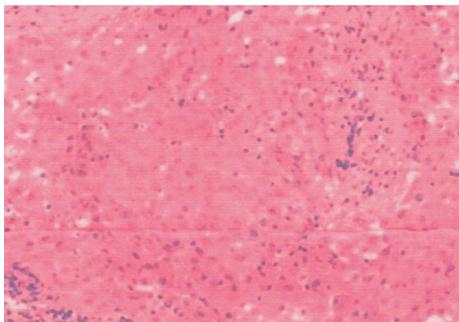
ultrasound biomicroscopy (UBM) examination showed ciliary detachment of the right eye (Figure 7). The thorax CT found shadows in the left upper lung (Figure 4D). The crizotinib was discontinued and the second generation anti-ALK agent, AP26113 was initiated. After AP26113 treatment, the patient's ocular symptoms were resolved and vision improved. The



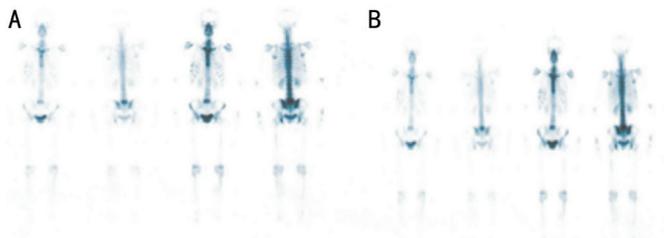
**Figure 3 Magnetic resonance imaging** A: MRI scan revealed an intraocular lesion at the initial presentation; B: MRI showed the ocular mass on the 16<sup>th</sup> month of crizotinib therapy.



**Figure 4 Thorax CT** A: A nodule in the left upper lung; B: Regression of the primary lesion on the 4<sup>th</sup> month; C: No progression of malignancy on the 16<sup>th</sup> month of crizotinib therapy; D: Shadows in the left upper lung on the 17<sup>th</sup> month.



**Figure 5 Lymph node biopsy confirmed an adenocarcinoma.**

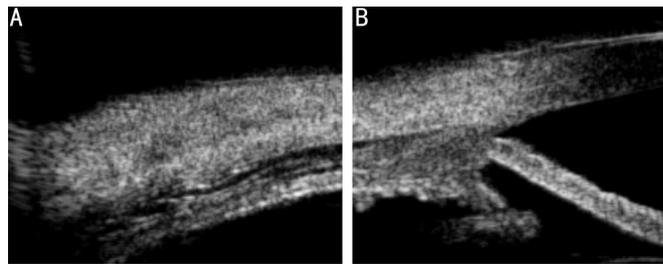


**Figure 6 PET-CT** A: Revealed positive signals on the right side of No. 6 and No. 7 ribs and on the left side of acetabulum; B: No progression of malignancy on the bones on the 16<sup>th</sup> month of therapy.

height of the new choroidal metastasis decreased soon after the initiation of therapy (Figure 2G, 2H). The funduscopy image showed regression of the new metastasis (Figure 1E). At the time of this case report, the patient has been on AP26113 therapy for over 10wk and was stable with 20/60 vision.

#### DISCUSSION

Choroidal metastasis may be a sign of a relapse of a known primary malignant neoplasm or the initial presentation of an



**Figure 7 Ultrasonic biomicroscopy revealed ciliary edema without ciliary metastasis.**

unknown primary malignant neoplasm<sup>[6]</sup>. The incidence of ocular metastases is likely underestimated, because patients suffering from systemic carcinoma are frequently so ill that they ignore or are unaware of ocular symptoms<sup>[10]</sup>. Metastasis to the ocular structures occurs by haematogenous spread, and therefore parts of the eye with the best vascular supply are most likely to be affected. Thus, choroid is the most common site of ocular metastasis<sup>[11]</sup>. In patients with uveal metastasis from all primary sites, 34%-44% had no known history of cancer at the time of ocular diagnosis. Most were identified with lung cancer as the primary cancer site, usually accompanied with brain metastasis, representing an advanced stage and worse survival prognosis<sup>[12]</sup>. The goal of therapy is to restore visual acuity, and therefore improve the quality of life for the patient's remaining life. The standard treatment is external beam radiotherapy, applying 30 Gy in 10 fractions or 40 Gy in 20 fractions. The reported complete response and improved visual acuity rates are 80% and 57%-89%, respectively<sup>[13]</sup>. But visual preservation after external beam radiotherapy is only short-term due to potential long-term side effects such as cataract formation and radiation retinopathy<sup>[14]</sup>. Intravitreal bevacizumab (IV-Bev) is a newer modality being employed for local control of symptomatic choroidal metastases. However, the role of maintenance IV-Bev in preventing ocular relapses and whether all patients with symptomatic choroidal metastases need local therapy in addition to systemic therapy remain unanswered questions<sup>[15]</sup>. In Shah *et al's*<sup>[2]</sup> report on clinical presentation, treatment, and outcome in 194 patients with uveal metastases from lung cancer, the systemic prognosis remains poor with tumor-related death in 54% of patients at 1y. Disease progression was most common<sup>[16]</sup>. Advances at the molecular level and genetics led to the recognition of multiple molecularly distinct subsets of NSCLC. The rationally directed molecular targeted therapy led to improved clinical outcomes<sup>[5]</sup>. Chinese and other Asian patients treated with the targeted therapy seem to have lower toxicity and higher efficacy compared with other ethnicities<sup>[17-18]</sup>. ALK-rearranged adenocarcinoma represents about 5%-7% of NSCLC<sup>[7]</sup>. It is seen in up to 33% of patients with NSCLC after exclusion of EGFR and kirsten rat sarcoma viral oncogene (KRAS) mutation<sup>[19]</sup>. The echinoderm microtubule associated protein-like 4 (EML4) gene fused to the ALK gene was first identified as a potentially targetable oncogenic driver in non-

small cell lung cancer in 2007<sup>[20]</sup>. The EML4-ALK fusion transcript is a promising candidate for the targeted therapy as well as for a diagnostic molecular marker in NSCLC. ALK inhibitors include crizotinib, and more recently ceritinib and alectinib<sup>[21]</sup>. Crizotinib demonstrated a response rate of 56% and a disease control rate of 87% in previously treated patients<sup>[22]</sup>. In 2014 Bearz *et al*<sup>[7]</sup> reported the first case of choroidal metastasis responding to crizotinib without previous radiotherapy, suggesting crizotinib alone may suffice in patients harboring ALK translocation. Lu *et al*<sup>[9]</sup> recently presented a patient with receptor tyrosine kinase 1 (ROS1)-rearranged NSCLC that presented with choroidal metastasis that did not respond to the initial chemotherapy but had a rapid and complete response to crizotinib. These reports together with our case report demonstrate that the targeted therapy, with excellent efficacy data and safety profile, is likely to be the preferred treatment choice in the rare incidence of ALK- and ROS1-rearranged NSCLC patients presenting with choroidal metastases. In our case the second generation of ALK inhibitor controlled the new metastasis after crizotinib resistance development. Our case confirmed that AP26113 was well tolerated with preliminary antitumor activity in ALK-positive patients, in whom crizotinib treatment previously failed<sup>[23]</sup>.

The ocular metastasis responds quickly to rationally directed molecular targeted therapy possibly through the fenestrated endothelium of choroidal vessels<sup>[7]</sup>. It was previously suggested that an ocular oncologist is able to monitor the response to systemic treatment most effectively because the regression of uveal metastases can be observed directly, unlike metastases in other parts of the body. In our case the resistance to crizotinib was discovered due to the new ocular metastasis development, while the primary site in the lung and the bone metastases remained stable. This is contrary to Bearz *et al*'s<sup>[7]</sup> report that the primary site tumor increased while the choroidal metastasis were still stable because in that case the patient received endolaser treatment and vitrectomy to cure the retinal detachment. Our case suggests that the changes in choroidal metastasis can reflect the systemic therapy. Because of this, we suggest that in the patients with NSCLC presenting initially with choroidal metastasis, local therapy should be refrained in the early stage so the ocular oncologist can monitor the response to systemic targeted treatment based on changes in choroidal mass. Early detection of drug resistance through the choroid reaction may change the systemic and ocular outcome<sup>[24]</sup>.

## CONCLUSION

The choroidal metastasis is not only possibly the first sign of a relapse of a known or unknown primary malignant neoplasm, but also can be the first sign of therapy resistance. The ocular metastasis as the initial presentation of NSCLC responds quickly to targeted systemic therapy. There are putative and in-

novative therapeutic approaches that are on going to overcome acquired resistance. We recommend withholding local therapy initially so that the ocular response can be monitored as an indicator of systemic therapy efficacy.

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