Choroidal Metastases Responsive to Crizotinib Therapy in a Lung Adenocarcinoma Patient with *ALK* 2p23 Fusion Identified by ALK Immunohistochemistry

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CASE

A 62-year-old never-smoker African American woman presented with flashing lights and floaters in the left eye in July 2011. Ophthalmic examination revealed visual acuity of 20/20 in her right eye and counting fingers in the left. Multiple lobulated, yellowish choroidal masses in the left eye with overlying subretinal fluid, and two smaller lesions in the right eye were identified (Fig. 1*A*). The clinical findings were highly suggestive of choroidal metastases. She underwent positron emission tomography and body computed tomography scans, which revealed a 2.1 × 4.5 cm left lower lobe lung mass, with probable angiolymphatic carcinomatosis in mid left lung and diffuse adenopathy from neck to pelvis (maximum standardized uptake value 10.6) (Figure 2A). Bronchoscopic lung mass biopsy revealed adenocarcinoma consistent with lung primary. Brain magnetic resonance imaging result was negative. Clinical tumor testing for *EGFR* mutation and *ALK* 2p23 translocation by fluorescence in situ hybridization (FISH) both returned originally reported as negative. *ALK* FISH assay was performed before approval by the Food and Drug Administration (FDA) as the companion diagnostic assay for crizotinib (Abbot Molecular Vysis *ALK* Break Apart Probe Kit; Abbott Molecular, Abbott Park, IL), which demonstrated 22% cells having two fusion signals and one red signal but no green signals (2F1R0G), an atypical pattern originally classified as negative for a classic gene rearrangement.

The patient was begun on standard chemotherapy carboplatin area under the curve 6 and pemetrexed 500mg/m^2 in August 2011. She tolerated treatment poorly and was found to have tumor progression including diseases in the eyes after the third cycle. Palliative radiation (RT) was then delivered to both eyes (30 Gy in 10 fractions) but with no resultant clinical response. Interestingly, she subsequently experienced good partial response and palliative benefit to second-line erlotinib. However, this was followed by systemic progression after 5 months of erlotinib (Fig. 2*B*), whereas the choroidal metastases remained stable.

During the course of our ongoing translational research study evaluating ALK immunohistochemistry (IHC) as a potential diagnostic assay in *ALK* 2p23 translocated (ALK+) lung cancer, her original tumor was found to be ALK IHC (+) (Fig. 3). *ALK* FISH test was repeated by using same assay and again demonstrated an atypical rearrangement (34% cells having 2F1R0G signal pattern). The recent FDA-approved *ALK* FISH assay interpretative criteria classify the atypical 2F1R0G pattern as positive for *ALK* rearrangement (>15% cells). The patient was therefore started on crizotinib in April 2012, and had significant symptomatic improvement and radiographic near-complete response after 4 months, lasting up to the present (18 months) (Fig. 2*C*). Strikingly, her left vision improved to 20/40, with ocular ultrasound imaging showing no detectable lesion after 10 months of therapy (Fig. 1*B*). She currently remains on crizotinib with excellent tolerance.

DISCUSSION

Lung cancer is the second most common malignancy. Choroidal metastasis from lung cancer is known to occur, although as a rare presentation.[1,2] The response of choroidal metastases to systemic chemotherapy or radiation has also been reported.[3] Our case report is the first to describe a patient who had dramatic simultaneous systemic and ocular disease response to crizotinib, an ALK-tyrosine kinase inhibitor, which targets ALK+ lung cancer.[4] The remarkable tumor response to crizotinib in choroidal metastases as reported here suggests excellent drug delivery to choroid. The patient's dramatic response during crizotinib therapy is unlikely a late effect of radiation, which was completed 6 months before.

ALK FISH is the FDA-approved companion diagnostic test for *ALK* 2p23 translocation. However, atypical FISH

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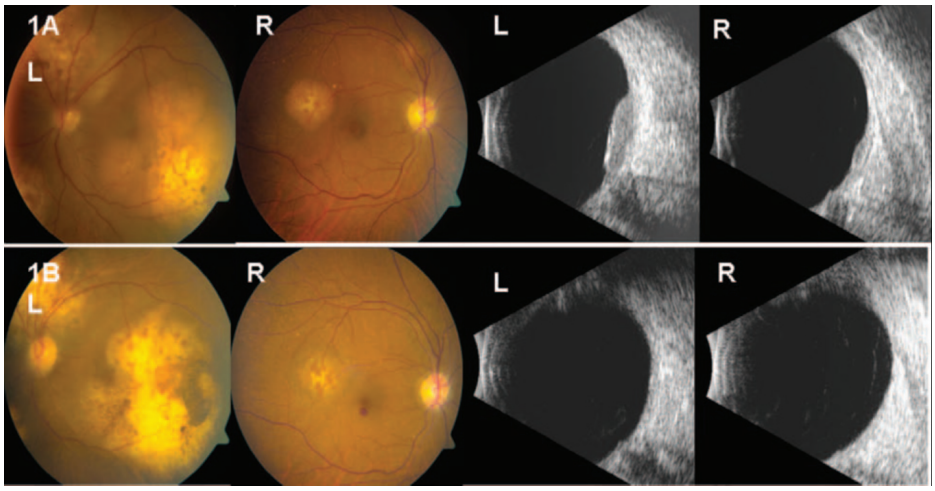

FIGURE 1. Retinal images and ocular ultrasonography of patient's left (L) and right (R) eye at diagnosis (1A, top) and after 10 months of crizotinib therapy (1B, bottom).

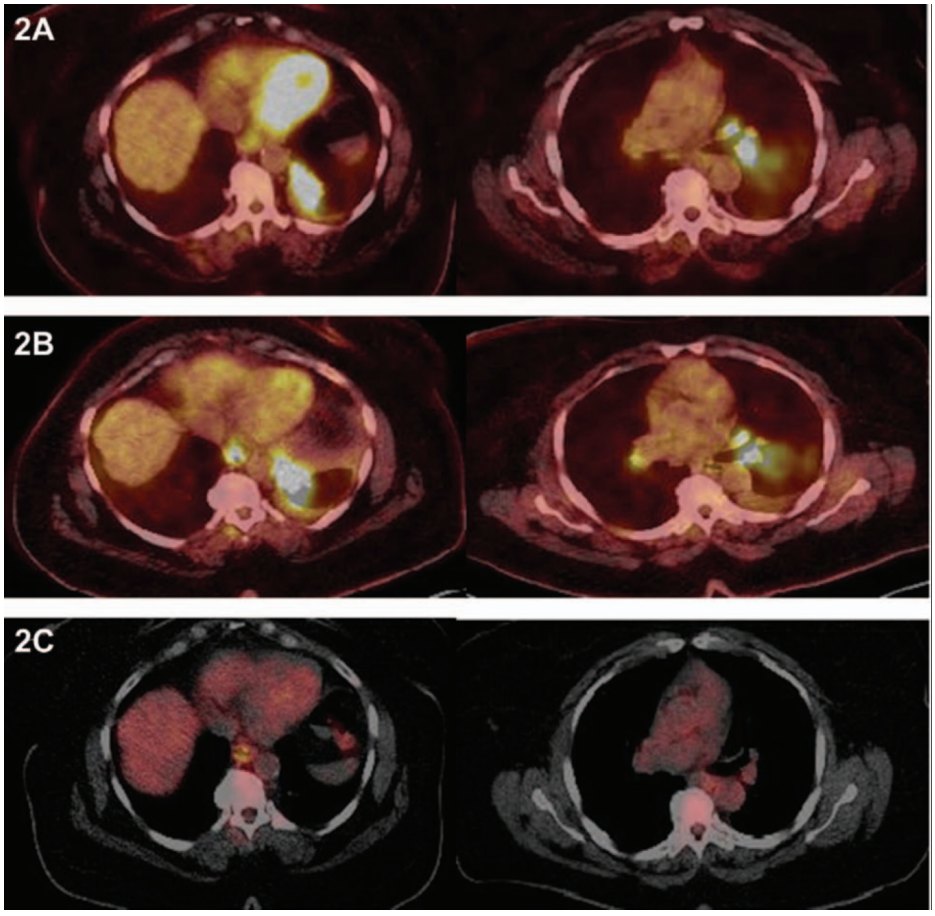

FIGURE 2. PET/CT scans indicating patient's left lower lobe mass and left hilar adenopathy at diagnosis (2A), progression after 5 months of erlotinib (2B) and complete response after 14 months of crizotinib (2C).

patterns such as 2F1R0G in our case must be recognized as variant rearrangements qualifying patients for crizotinib. We also emphasize that not all atypical *ALK* rearrangements are productive of the endocoded protein; specifically, a 1F1G0R atypical rearrangement is classified as FISH negative. We recently evaluated an ultrasensitive automated IHC in the diagnosis of ALK+ non-small cell lung cancer, comparing it with *ALK* FISH and demonstrated 100% sensitivity and specificity.[5] ALK IHC could be a cost-effective screening test to supplement *ALK* FISH in lung cancer targeted therapy.

REFERENCES

1. Shields CL, Shields JA, Gross NE, Schwartz GP, Lally SE. Survey of 520 eyes with uveal metastases. *Ophthalmology* 1997;104:1 265–1276.

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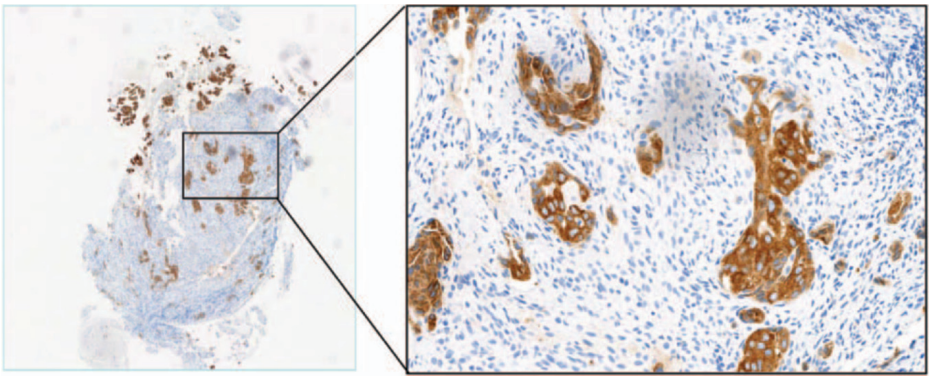

FIGURE 3. ALK immunohistochemistry (IHC) expression analysis on patient's tumor (left: 4X, right: 20X).

2. Kreusel KM, Bechrakis NE, Wiegel T, Krause L, Foerster MH. Incidence and clinical characteristics of symptomatic choroidal metastasis from lung cancer. *Acta Ophthalmol* 2008;86:515–519.
3. Singh N, Kulkarni P, Aggarwal AN, et al. Choroidal metastasis as a presenting manifestation of lung cancer: a report of 3 cases and systematic review of the literature. *Medicine (Baltimore)* 2012;91:179–194.
4. Shaw AT, Engelman JA. ALK in lung cancer: past, present, and future. *J Clin Oncol* 2013;31(8):1105–1111.
5. Minca EC, Portier BP, Wang Z, et al. ALK status testing in non-small cell lung carcinoma: correlation between ultrasensitive IHC and FISH. *J Mol Diagn* 2013;15:341–346.

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