Correspondence

Ipsilateral breast metastasis from lung adenocarcinoma harboring anaplastic lymphoma kinase or ROS1 rearrangement and significant response after targeted therapy: report of two cases

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To the Editor: A 43-year-old female patient was admitted to our department for a 6-month-history of paroxysmal cough in July 2013. She was diagnosed with right lower lung adenocarcinoma (cT2aN3M1b, stage IV, anaplastic lymphoma kinase [ALK]+) with bone metastasis in other hospital and came to participate a phase III trial of crizotinib (NCT01639001).

Computed tomography (CT) scan revealed a mass in the right lower lung, two masses in the right breast located in lower and outer quadrant, upper and inner quadrant separately. We further identified the nature of two masses in the right breast by needle biopsy. Immunohistochemistry (IHC) showed ALK(+), thyroid transcription factor-1 (TTF-1) (+), ALK(−), G-15(−), TTF-1(−), NapsinA(+), P63(−), estrogen receptor (ER)(−), PR(−), CerbB-2(−), P53(+), CK5(+), E-cadherin(+), Ki-67(−), MMG(−) both in the cancer tissues of right breast and in the right supraclavicular lymph node [Figure 1E–G]. FISH using a probe specific to the ROS1 locus (Vysis locus specific identifier ROS1 dual-color, break-apart rearrangement probe; Abbott Molecular, Abbott Park, IL) also showed ROS1 translocation [Figure 1H]. The patient was diagnosed as lung adenocarcinoma with multiple metastases including breast, bone, and brain (T4N3M1b stage IV) harboring ROS1 rearrangement.

The patient was then enrolled in the clinical trial and assigned to the chemotherapy group on August 1, 2013. It showed progression disease after 12 weeks of chemotherapy. She received whole brain radiotherapy in December 2013 and crossed over to crizotinib group on January 22, 2014. The patient had a partial response (PR) with significant shrinkage of the tumor lesion in lung, brain, and the disappearance of the tumor lesions in breast. The efficacy of crizotinib persisted to August 9, 2017 for the enlargement of lung lesion and new brain lesions. She participated in another clinical trial (NCT03215693) and received the treatment of x-396 treatment since December 19, 2017. The brain metastases were significantly shrunk and the lung lesion was stable. The patient died in August 2019 for meningeal metastasis while the lung and breast lesions were still stable at death.

Another patient was a 44-year-old woman, who was admitted to our department with a 6-month history of progressive increase cough in March 2014. CT scan revealed one mass in the right lower lung, enlarged lymph nodes in mediastinum and retroperitoneal, one mass in the right breast located in lower and outer quadrant, upper and inner quadrant separately. The patient was then enrolled in a Phase II study of crizotinib (NCT01945021). She received crizotinib treatment from April 15, 2014 and got a PR with significant shrinkage of the central nervous system lesions in breast [Figure 1I and 1J]. However, there was no obvious improvement of the central nervous system lesions and she died 8 months later. Breast metastasis from extra-mammary malignancies is rare and it just makes up approximately 2% of all malignant mammary neoplasms.[1]

ER, PR are the representative markers of primary breast cancer and TTF-1 was the immunoreactive markers for lung adenocarcinoma.[2] Previous studies have reported

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that epidermal growth-factor receptor (EGFR) mutations were detected in both primary cancer and breast metastases. In our cases, both the primary lung lesion and breast metastases are immunohistochemically positive for ALK or ROS1 rearrangement, and the rearrangements were both confirmed by FISH. We believed that driven genes mutations, including EGFR/ALK/ROS1, were useful biomarkers to identify primary breast cancer from lung cancer breast metastases.\(^3\)

What’s more, targeted tyrosine kinase inhibitor, crizotinib, has been approved by the FDA to treat non-small cell lung cancer patients with ALK or ROS1 rearrangement. It has a response rate of nearly 60% and 7.7 to 8.1 months median progression-free survival (PFS) in ALK positive patients and a 72% objective response rate and 19.2 months median PFS in ROS1 positive patients.\(^4,5\)

It is important to detect EGFR/ALK/ROS1 gene mutation in patients with both lung and breast lesions to identify which is the primary lesion and make more precise treatment.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

None.

**References**


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*Figure 1: The breast tumor cells diffusely expressed positive TTF-1 (A and E, TTF-1 immunostaining, original magnification ×200), negative G15 (B and F, G15 immunostaining, original magnification ×200) and positive ALK (C, ALK immunostaining, original magnification ×200) and ROS1 (G, ROS1 immunostaining, original magnification ×200). FISH result using break-apart probes showed ALK rearrangement (D, splitting of green and orange signals) and ROS1 rearrangement (H, splitting of green and orange signals). CT scan revealed the mass in the right lower lung, mass in the right breast, and pleural effusion (I); both the lung mass and the breast mass were significantly shrunk after 6 weeks treatment of crizotinib (J). ALK: Anaplastic lymphoma kinase; CT: Computed tomography; FISH: Fluorescence in situ hybridization.*