Case presentation

In February 2013, a 68-year-old never smoker female patient with paroxysmal primordial pain underwent a computed tomography (CT) scan and detected a $20 \times 15$ mm mass in basal segments of the lower lobe of the right lung (Figure 1).

A right lower lobectomy of the CT detected mass and a lymph node dissection were performed to further determine the pathological feature. The histopathological analysis led to the diagnosis of NSCLC consistent with moderately differentiated adenocarcinoma and pathologic staging was T1N0M0, clinical stage IA (AJCC version 6). There was no residual tumor on histological examination, and the patient did not receive any adjuvant therapy.

The patient returned to our hospital in February 2016, presented with progressive lumbago that had been ongoing for 3 months. Multi metastases
were detected in the right lower lobe and liver on CT of the chest and abdomen (Figure 2(a)). In addition, bone scan revealed multiple bone metastases (Figure 2(b)). The patient received zoledronic acid for the treatment of bone metastases. The surgically removed tumor tissue specimen revealed an activating L858R mutation in exon 21 of epidermal growth factor receptor (EGFR) using a amplification-refractory mutation system (ARMS)-based AmoyDx EGFR 29 Mutation Detection Kit; the patient was promptly initiated of gefitinib 250 mg once daily in the first-line treatment setting, but a poor response was observed. CT scan showed progressive disease with rapid growth of lung and bone metastasis after 3 weeks of this regimen (Figure 3(a) and (b)).

The patient was recommended for a next-generation sequencing (NGS) comprehensive genomic profiling to reveal more drug targets since she declined to receive more chemotherapies. Her surgically resected tumor tissue and matched blood sample were subsequently sent for NGS panel sequencing after consent obtained from the patient herself and her family.

The comprehensive genomic profiling analyses various types of genomic alterations, including base substitutions, insertions and deletions, copy number alteration, and rearrangements on genes commonly associated with cancers. The NGS analysis revealed an EGFR L858R mutation and HER2 S310Y mutation. Preclinical study suggested that novel occurring HER2 extracellular domain mutations such as S310Y was potently oncogenic, and S310Y mutant was abrogated by treatment with small-molecule inhibitors of HER2.1 Afatinib is an irreversible inhibitor directly against both EGFR and HER2. Afatinib was prescribed as a second-line therapy at 40 mg once daily. Although clinical response with resolution of lumbago was observed after 2 weeks, the administration of Afatinib was stopped due to grade 3 gastrointestinal toxicity. The patient died 3 months after the diagnosis of recurrence of lung cancer.

Discussion

Previous large clinical trials demonstrated that approximately 70% of advanced NSCLC patients with EGFR-activating mutations displayed responses to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). However, the
remaining 30% of EGFR-positive patients do not response to EGFR-TKIs. Recently, increasing numbers of novel genomic alterations such as T790M mutation, MET amplification, ALK fusion, and BIM deletion have been discovered by NGS comprehensive genomic analysis, which contributed to primary resistance of EGFR inhibitors in EGFR-positive NSCLC patients novel.3

HER2 amplification was considered as one of the known mechanisms of acquired EGFR-TKIs resistance in NSCLC patients. However, HER2 amplification could be detected in both pre or post TKIs treatment patients, which indicates that it is also a clinical important primary resistance factor for EGFR-TKIs.4–6 Not only amplification, single-nucleotide variations (SNVs) and insertion/deletion (InDel) on HER2 were found in approximately 2%–5% samples with lung adenocarcinomas in the TCGA database. Preclinical models suggest that HER2 kinase domain mutation results in constitutive phosphorylation and activation of HER2 and EGFR and resistance to EGFR-TKIs. Knockdown of HER2 G776VYMA insertion in lung cancer cell line increased apoptosis and restored sensitivity to EGFR-TKIs.7 HER2 S310Y mutation was found in 1 out of 258 (0.4%) lung adenocarcinomas sequenced by the Cancer Genome Atlas Network, which were potently oncogenic.1 Ba/F3 cell with HER2 extracellular domain mutant responds to EGFR/HER2 dual inhibitors afatinib and neratinib treatment.1,8

Here, we describe a case of an EGFR-positive NSCLC patient with a novel HER2 S310Y mutation who experienced primary resistance to gefitinib, afatinib which blocks both EGFR and HER2 was recommended as a second-line treatment.9,10 The patient’s clinical symptoms were in remission with afatinib administration but the treatment was unfortunately interrupted due to the gastrointestinal toxicity.

This is the first case report that suggests the role of HER2 S310Y in driving EGFR-TKIs resistance in EGFR-positive NSCLC patient. The clinical benefit of afatinib therapy for this subgroup of patients needs to be validated in future studies.

Declaration of conflicting interests
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