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Primary resistance to icotinib in a patient with lung adenocarcinoma harboring *EGFR* L858R and Q787k mutations

To the editor

Approximately 50% of patients with non-small-cell lung cancer (NSCLC) harbor epidermal growth factor receptor (*EGFR*) mutation in Asia, and the administration of EGFR-tyrosine kinase inhibitors (TKIs) has become the standard clinical therapeutic protocol [1]. Although most patients with *EGFR*-activating mutations responded well to EGFR-TKIs, primary resistance still occurred in approximately 5%–10% of the whole population [2]. Here we report a female patient with lung adenocarcinoma harboring *EGFR* L858R and Q787k mutations who exerted primary resistance to icotinib.

A 72-year-old woman with the complaints of paroxysmal cough and persistent blunt pain in her right lower chest was admitted to hospital. Chest CT revealed an unclear structure of the right lung hilum accompanied with bronchial stenosis and atelectasis in the middle lobe. Other abnormalities included scattered inflammation in both lungs, enlargement of the mediastinal lymph nodes, and pleural effusion in the right side of the chest. Bronchoscopy was performed in the right lung and indicated a pathological diagnosis of lung adenocarcinoma. Chemotherapy comprising pemetrexed and carboplatin was administered as the first-line treatment, followed by pemetrexed monotherapy as the maintenance therapy. However, increasing pleural effusion was observed, indicating that the disease was not under control. In addition, tumor cells were found in the pleural effusion and metastasis was considered.

To determine potential therapeutic methods, the hydrothorax was subjected to next-generation sequencing analysis and *EGFR* L858R, an *EGFR*-sensitive mutation was identified, together with another unknown mutation, *EGFR* Q787 K (Fig. 1). Icotinib was immediately administrated; however, progressed disease was soon considered because of the progression of right lung and left kidney lesions (Fig. 2). Meanwhile, increasing pleural effusion and emerging pericardial effusion were observed in the patient, and primary resistance to EGFR-TKI was considered.

The mechanism underlying primary resistance to EGFR-TKIs is unclear and confusing for clinicians. Several studies have indicated that PIK3CA mutations [3], deletion polymorphisms of BIM [4], and *EGFR* exon 20 insertions [5] were associated with primary resistance to EGFR-TKIs. In our case, one unknown *EGFR* mutation, *EGFR* Q787 K, located in exon 20 of the *EGFR* gene was identified. Moreover, to understand the effect of *EGFR* Q787 K mutation on the spatial structure of *EGFR* L858R, we performed in-silico simulation (Fig. 3). The *EGFR* Q787 residue could originally form hydrogen bonds with residue C781, whereas the K787 residue could form extra hydrogen bonds with residues T783 and E746, as well as residue C781. The redundant hydrogen bonds might yield a more stable and condensed structure of the ligand-binding area of the mutant EGFR protein than wild type EGFR, which might interrupt the interaction between icotinib and *EGFR* L858R, leading to the primary resistance.

To date, this is the first case report of the coexistence of *EGFR* Q787 K and L858R mutations in a patient with lung adenocarcinoma who showed primary resistance to icotinib. Our case may provide useful information for the better understanding of the primary resistance of EGFR-TKI and facilitate more precise administration of EGFR-TKIs in clinical practice.

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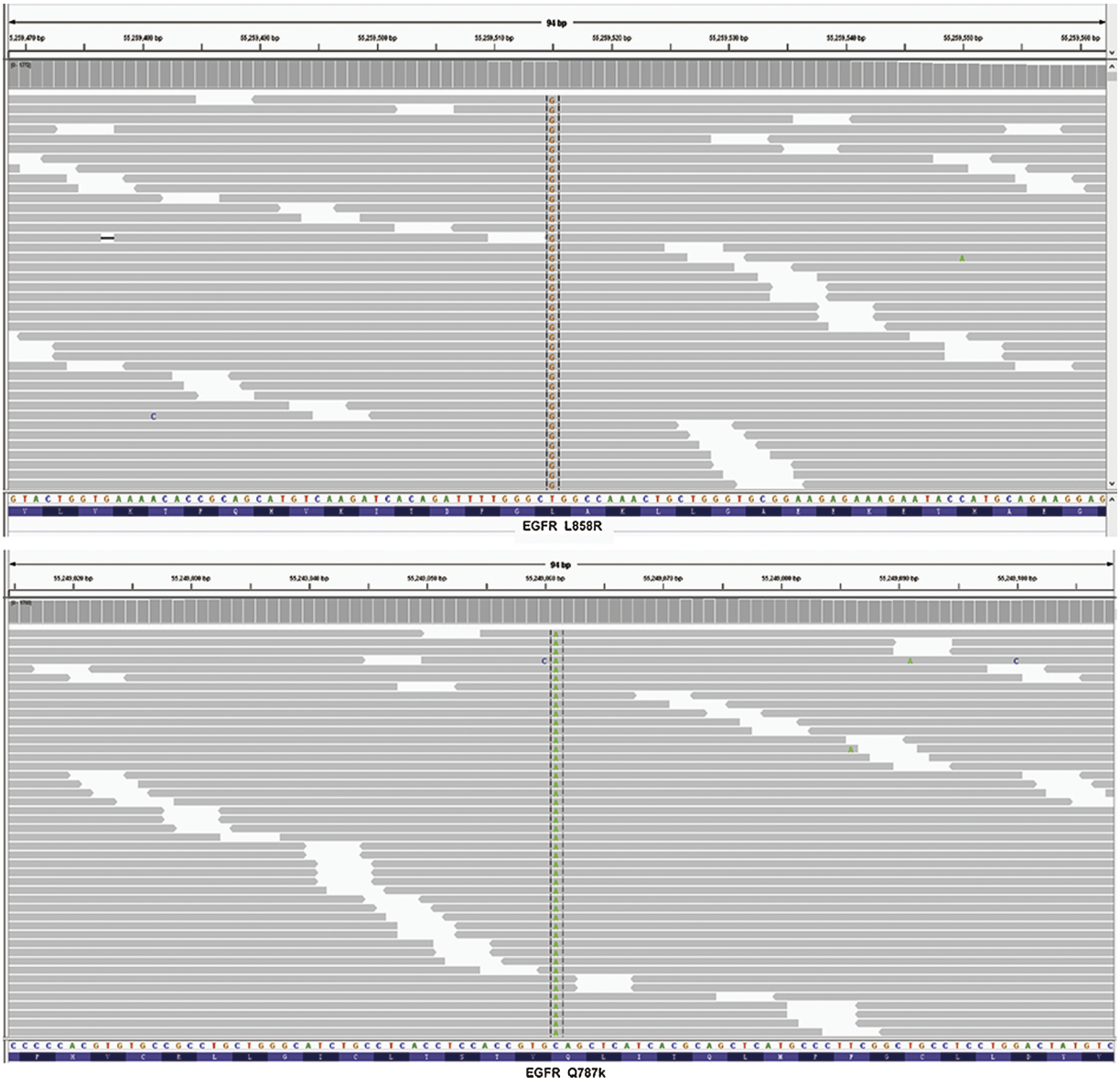

Fig. 1. Next-generation sequencing (NGS) results of the pleural effusion sample. Two mutations, EGFR L858R and Q787 K, were identified.

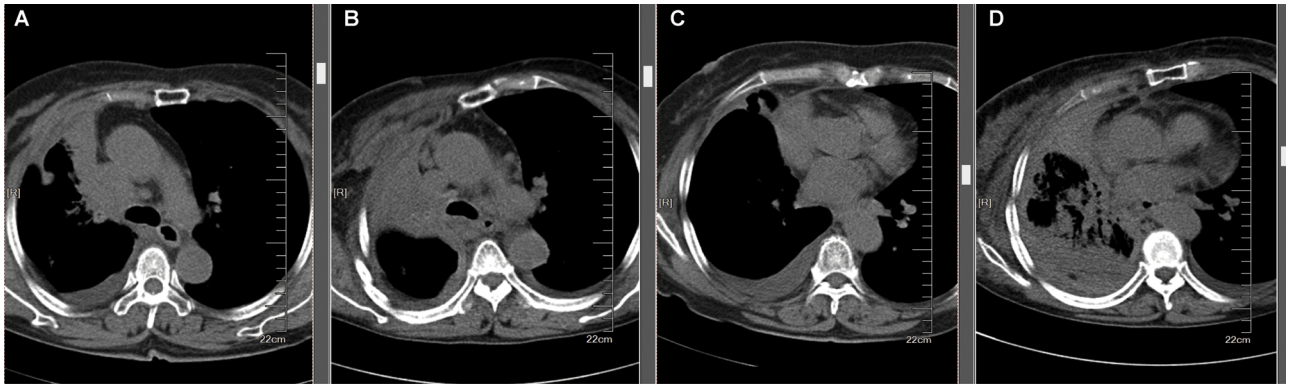

Fig. 2. Tumor response of the patient's right lung and left kidney lesions during icotinib treatment. (A) Tumor lesion in the right lung increased after 3 months of icotinib treatment. (B) Tumor lesion in the left kidney increased after 3 months of icotinib treatment.

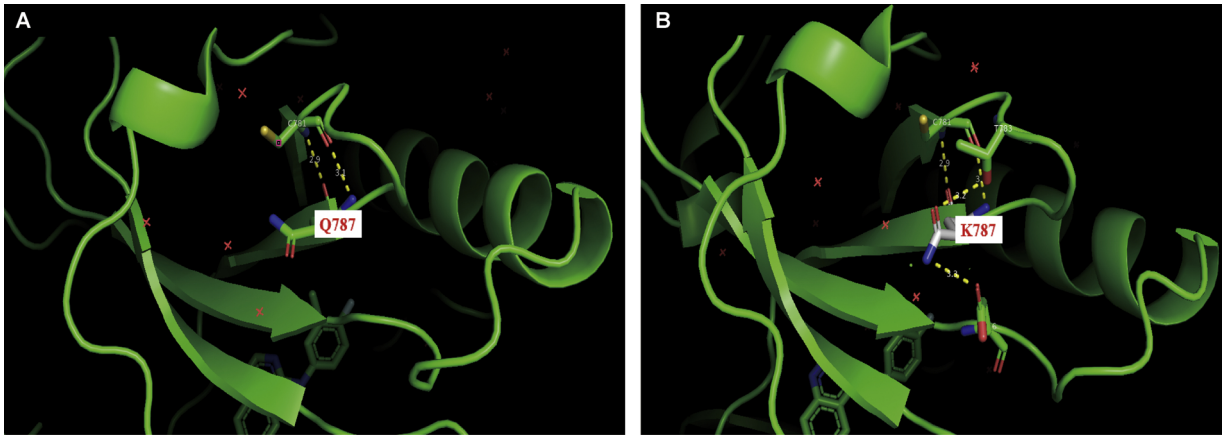

Fig. 3. Structural analysis of EGFR L858R and Q787 K mutants. The EGFR Q787 residue could originally form hydrogen bonds with residue C781. When EGFR Q787 K mutation was simulated, K787 residue could form extra hydrogen bonds with two additional residues, T783 and E746.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

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