Case Report

The effect of afatinib in a pretreated patient with invasive mucinous adenocarcinoma of the lung harboring *HER2* YVMA insertion: a case report

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Background: Invasive mucinous adenocarcinoma (IMA) is an uncommon variant of lung adenocarcinoma. The survival data and therapeutic methods for IMAs are limited. The frequency of human epidermal growth factor receptor 2 (*HER2*) mutations in IMAs is low, and the clinical benefit of HER2 inhibitors in patients with IMA is still being explored. Afatinib is a pan-HER inhibitor and the studies of afatinib treatment in IMA patients are very limited.

Case Description: Herein, we present the case of a 49-year-old female, never-smoker stage IVa IMA patient with persistent cough and sputum expectoration diagnosed with stage IVa IMA. Polymerase chain reaction (PCR) and next-generation sequencing (NGS) were utilized to detect mutations for targeted therapies on lung biopsy, but no mutation was found. After treatment failures of chemotherapy and a multiple-kinase inhibitor, liquid biopsy identified *HER2* exon 20 insertion p.A775_G776insYVMA with NGS. The patient was then treated with afatinib as the third-line treatment. Following administration for one month, the patient's symptoms of coughing, sputum expectoration, and dyspnea improved. Stable disease (SD) was observed, and the patient achieved durable clinical benefit with prolonged progression-free survival (PFS) of 20 months. Her overall survival was 5.8 years.

Conclusions: This is the first report of afatinib treatment achieving long-lasting and stable disease control in an IMA patient with a *HER2* exon 20 YVMA insertion. Our results will help to improve the treatment of IMA.

Keywords: Afatinib; invasive mucinous adenocarcinoma (IMA); *HER2* exon 20 insertion; YVMA insertion; case report

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Introduction

Lung cancer is the leading cancer in mortality and morbidity globally, and adenocarcinoma is the most common histological type of lung cancer (1). Invasive mucinous adenocarcinoma (IMA) is an uncommon histologic subtype, accounting for approximately 2–10% of lung adenocarcinomas (2). IMAs are associated with a high recurrence rate and are more malignant than most common types of lung adenocarcinoma, such as acinar or papillary adenocarcinoma (3). However, IMA's survival data and therapeutic methods are insufficient due to their low incidence and the lack of consensus on treatment (4-6).

Genetically, IMAs have a low mutation burden and often have a single identifiable driver mutation, e.g., *KRAS*, *BRAF*, *ERBB2*, *PIK3CA* mutations, and *NRG1*, *NTRK1*, *ALK*, *RET*, and *ERBB4* rearrangements (7,8). *KRAS* mutations were the most commonly detected driver mutations (9,10). The frequency of human epidermal growth factor receptor 2 (*HER2*) mutations in IMAs is low. Several studies have reported the frequency of *ERBB2* (*HER2*) mutations in IMAs is about 1.23–6% (10,11). Afatinib is an ErbB family blocker, which covalently binds and irreversibly

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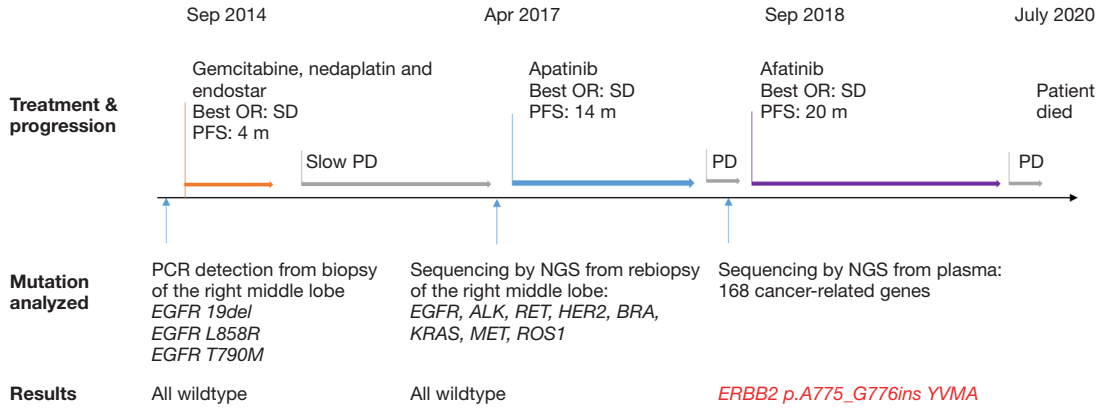

Figure 1 Timeline of disease management, showing different treatments and the results of mutation analyses. Abbreviations: OR, overall response; SD, stable disease; PFS, progression-free survival; PD, progressive disease; PR, partial response; PCR, polymerase chain reaction; NGS, next-generation sequencing.

blocks epidermal growth factor receptor (*EGFR*) and *HER2*. Afatinib is modestly active in lung adenocarcinoma patients harboring *HER2* mutation, though conclusions and recommendations for its clinical use remain controversial due to the small sample size of these series (12-14). And the studies of afatinib treatment in IMA patients are very limited. Here we report a previously treated IMA patient with a *HER2* exon 20 insertion, who benefited from afatinib treatment. We present the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1457/rc).

Case presentation

A 49-year-old female, never-smoker, presented with persistent cough and sputum expectoration for one year in September 2014. She was treated with cephalosporins without curative effect. On admission, results of blood, urine, and stool routine tests were normal. The serum levels of tumor markers, carcinoembryonic antigen, carbohydrate antigen 125, squamous cell carcinoma antigen, neuron-specific enolase, and cytokeratin 19 fragment, were all normal. Chest computed tomography (CT) scan showed a 10.3 cm mass in the right middle lobe and multiple nodules in both lungs. Imaging with CT and bone scan revealed no distant metastases. The patient underwent a fine-needle biopsy of the right middle lobe. Histopathology confirmed an IMA. Immunohistochemically, tumor cells in the main part were CK7 (+), CK20 (+), CDX2 (+), TTF1 (+), Napsin A (+), and Ki67 (+10%). She was classified as stage IVa (T4N0M1a). Polymerase chain reaction (PCR) was utilized to detect mutations of exons 19, 20, and 21 of the *EGFR*, and no mutation was found. A combination of gemcitabine, nedaplatin, and endostar was administered in September 2014 (*Figure 1*). The patient achieved a stable disease (SD) after two months' treatment. Then she opted to receive no further treatment after three cycles. A follow-up CT scan showed progressive disease (PD), and she refused any chemotherapy. The patient underwent cholecystectomy because of acute acalculous cholecystitis in July 2015. Slow PD was further observed on CT.

The patient was hospitalized due to productive cough, sputum expectoration, and dyspnea in April 2017. Rebiopsy of the right middle lobe was taken, and histopathology test showed the same IMA as the first time. To screen for new treatment targets, targeted next-generation sequencing (NGS) consisting of 8 genes (*EGFR*, *ALK*, *RET*, *HER2*, *BRAF*, *KRAS*, *MET*, *ROS1*) was performed on lung rebiopsy sample, but no mutation was detected. A multi-kinase inhibitor apatinib (500 mg/day) was initiated in the same month. The patient achieved a partial response (PR) with a progression-free survival (PFS) of 14 months. The treatment was discontinued because of disease progression.

The patient's performance status (PS) score was 4 when apatinib was discontinued. Chest CT scans revealed a marked increase in lung nodules size in September 2018. CT showed multiple nodules in both lungs, with mixed airspace consolidation, air bronchogram, cavitation, and bulging fissure (*Figure 2*). No other metastatic lesions were observed in the rest of the body. Using a targeted panel consisting of 168 cancer-related genes (Burning Rock Biotech Ltd., Guangzhou, China), NGS profiling identified

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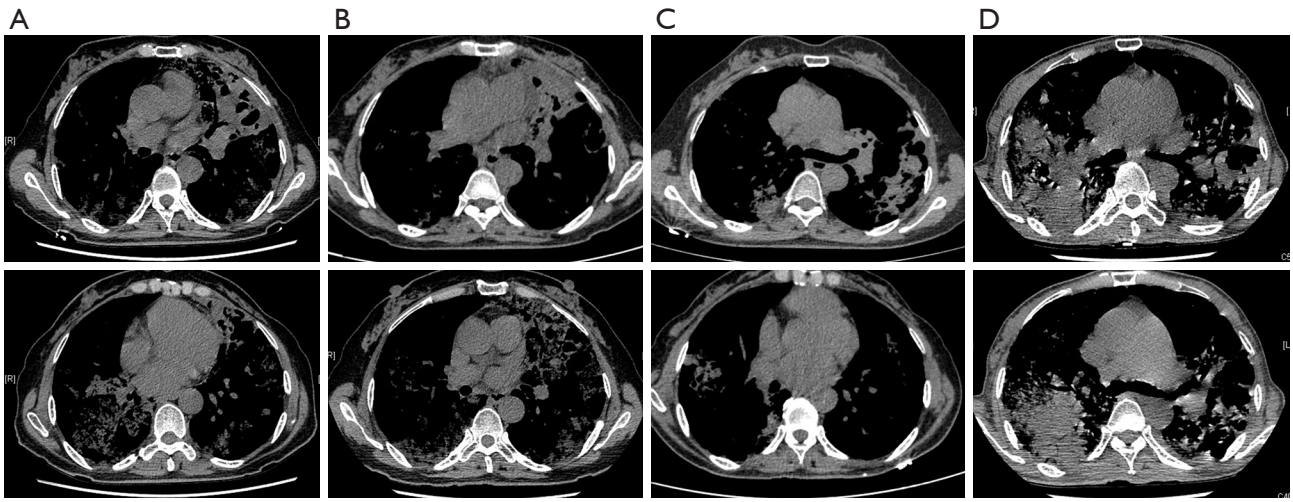

Figure 2 Computed tomography images showing response to afatinib treatment. (A) Pretreatment of afatinib in September 2018; (B) after 1 month of treatment with afatinib; (C) after 12 months of treatment with afatinib; (D) after 22 months of treatment with afatinib.

HER2 exon 20 insertion p.A775_G776insYVMA (YVMA insertion) in the plasma sample and the variant allele frequency (VAF) was 0.09%. The patient was subsequently treated with afatinib (40 mg/day). Following administration for one month, the patient's symptoms of coughing, sputum expectoration, and dyspnea improved. SD was observed on the CT scan (*Figure 2*). Treatment led to a regression in lung consolidations. The patient achieved durable clinical benefit with a prolonged PFS of 20 months, and her PS score was 1–2 during early treatment. In June 2020, a CT scan showed PD, and afatinib treatment was discontinued. During the late course of treatment, the patient experienced repeated lung infection and heart failure with a PS score of 3–4. The patient opted to receive no further treatment and died in July 2020 in a hospice. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In this case, a 49-year-old female, never-smoker, was diagnosed with clinical stage IVa IMA of the lung. A combination of gemcitabine, nedaplatin, and endostar was administered for three cycles, and SD was achieved. Apatinib was taken as the second-line treatment and showed a good response with a PFS of 14 months. Liquid biopsy identified *HER2* exon 20 insertion p.A775_G776insYVMA with NGS, which was previously undetected. Afatinib was initiated as third-line therapy. The patient had SD for 20 months with afatinib treatment. Her overall survival from diagnosis of stage IVa disease was 5.8 years.

IMA is rare and its clinical manifestations and prognosis are variable. Simsir et al. reported the main imaging findings of IMAs are lung nodules with multicentric, multilobar, and bilateral distribution and lower lung predominance (15). Mucinous adenocarcinomas are classified as pneumonic- and solitary-type tumors. Pneumonic-type IMA was defined as a tumor distributed extensively in the lung lobe. Beck et al and Sadohara et al. found spontaneous regression of airspace opacities in some IMA patients (16,17). The inconsistent CT findings on IMAs suggest it's challenging to assess tumor response with RECIST 1.1 in IMAs (16). In our case, the tumor lesions showed consolidation and ground-glass opacity (GGO) with diffuse distribution on CT images, which indicated the pneumonic-type IMA and made the tumor response hard to assess. The patient's symptoms improved quickly after afatinib treatment. The PS score was around 1–2 compared with four before afatinib treatment, which also indicated the excellent clinical efficacy of afatinib in IMA patients with *HER2* YVMA insertion.

The most common *HER2* mutation in lung adenocarcinoma is the YVMA insertion, in more than 50% of all *HER2* mutant patients (18,19). Afatinib has been

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approved for first-line therapy in patients with *EGFR*-mutated stage IV NSCLC. In a phase II trial of afatinib in patients with advanced NSCLC harboring *HER2* mutations, no clinical benefit of 12 weeks or longer was achieved with afatinib for EGFR TKI-naïve patients with *HER2* mutations (20). But they failed to collect or analyze the subtypes of *HER2* mutation in this study (20). A recent retrospective international multicenter study reported that the overall response rate of advanced lung cancers with *HER2*-mutation treated with afatinib was 13%, and all patients with clinical benefit harbored *HER2* exon 20 insertion (18). Patients with different *HER2* mutation subtypes showed different responses to afatinib treatment. Several other HER2-targeting agents have shown promise for NSCLC patients carrying *HER2* mutations, including T-DM1 and pyrotinib (21,22). However, when our patient intended to use anti-HER2 therapy, afatinib was still recommended by professional guidelines for *HER2* mutant NSCLC and was more readily available to the clinic. Further evidence will be gathered as more HER2 inhibitors are used in the clinical trial or in the routine clinical setting.

PCR and NGS were utilized to detect mutations for targeted therapies on lung biopsy, but no mutation was found. *HER2* YVMA insertion was identified with NGS on liquid biopsy with VAF as low as 0.09%. IMA is heterogeneous and presents with spatially separate lung lesions, which may lead to unreliable results of biomarker detection, notably when a single biopsy is tested (23). Detecting rare somatic mutations from a routine blood draw is highly challenging. Circulating tumor DNA (ctDNA) sequencing is being extensively investigated in the latest years, but variant detection was generally unreliable and variable among assays for mutations lower than 0.5% VAF (24). In our case, the ctDNA mutation detected before the third-line treatment was clinically meaningful with high sensitivity and precision. Ultrasensitive assays and repeated biopsies could better characterize cancer heterogeneity and better treatment options.

Conclusions

This is the first report of the afatinib treatment achieving long-lasting and stable disease control in the IMA patient with *HER2* YVMA insertion. *HER2* YVMA mutation may be a responsible variant for afatinib in IMA. The identification of novel medicines and therapeutic methods for IMA is urgent. Our results will help to improve the treatment of IMA.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1457/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1457/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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