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CASE REPORT

Combined Dacomitinib and Selpercatinib Treatment for a Patient with *EGFR*-Mutant Non-Small Cell Lung Cancer and Acquired *CCDC6-RET* Fusion

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Abstract: *RET* rearrangements are recognized drivers in lung cancer, representing a small subset (1–2%) of non-small cell lung cancer (NSCLC). Additionally, *RET* fusions also serve as a rare acquired resistance mechanism in *EGFR*-mutant NSCLC. Only a few NSCLC cases have been reported with co-occurrence of *EGFR* mutations and *RET* fusions as an acquired resistance mechanism induced by EGFR-tyrosine kinase inhibitors (TKIs). A 68-year-old man diagnosed with lung adenocarcinoma harboring *EGFR* L858R mutation initially responded well to dacomitinib, a second-generation EGFR-tyrosine kinase inhibitor (TKI). Afterward, he developed acquired resistance accompanied by a *RET* rearrangement. Next-generation sequencing (NGS) analysis revealed that the tumor possessed both the new *CCDC6-RET* fusion and the *EGFR* L858R mutation. Subsequently, he was treated with a combination of cisplatin, pemetrexed, and bevacizumab resulting in a partial response. Nevertheless, his condition deteriorated as the disease progressed, manifesting as hydrocephalus, accompanied by altered consciousness and lower limb weakness. The subsequent combined treatment with dacomitinib and selpercatinib resulted in a significant improvement in neurological symptoms. Here, we first identified acquired *CCDC6-RET* fusion with a coexisting *EGFR* L858R mutation following dacomitinib treatment. Our findings highlight the importance of NGS for identifying *RET* fusions and suggest the potential combination of dacomitinib and selpercatinib to overcome this resistance. For NSCLC patients with *RET* rearrangements and no access to RET inhibitors, pemetrexed-based chemotherapy provides a feasible alternative.

Keywords: NSCLC, RET rearrangement, EGFR mutation, dacomitinib, selpercatinib, NGS

Introduction

Dacomitinib, an irreversible second-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), has shown superior progression-free survival (PFS) and overall survival (OS) over gefitinib in patients with advanced non-small cell lung cancer (NSCLC) in the ARCHER 1050 study.[1,2] Nevertheless, despite high initial response rates, patients typically develop acquired resistance to dacomitinib treatment after approximately 1 to 2 years. *RET* rearrangements are recognized drivers in lung cancer, representing a small subset (1–2%) of NSCLC, and are also identified as a rare, acquired resistance mechanism in *EGFR*-mutant NSCLC.[3] There have been only a few reported NSCLC cases with coexisting *EGFR* mutations and *RET* fusions induced by EGFR-TKIs.[4,5] Here, we present a case of dacomitinib-induced *CCDC6-RET* fusion concurrent with an *EGFR* L858R mutation, successfully treated through a combination of dacomitinib and selpercatinib.

Case Presentation

A 68-year-old non-smoker male presented to the emergency department with a 2-month history of non-productive cough, dyspnea on exertion, weight loss, and progressive lower limb weakness. A chest X-ray (CXR) revealed a left-sided opacity (Figure 1A), and the contrast-enhanced chest computed tomography (CT) identified a 7 x 7 cm mass in the left

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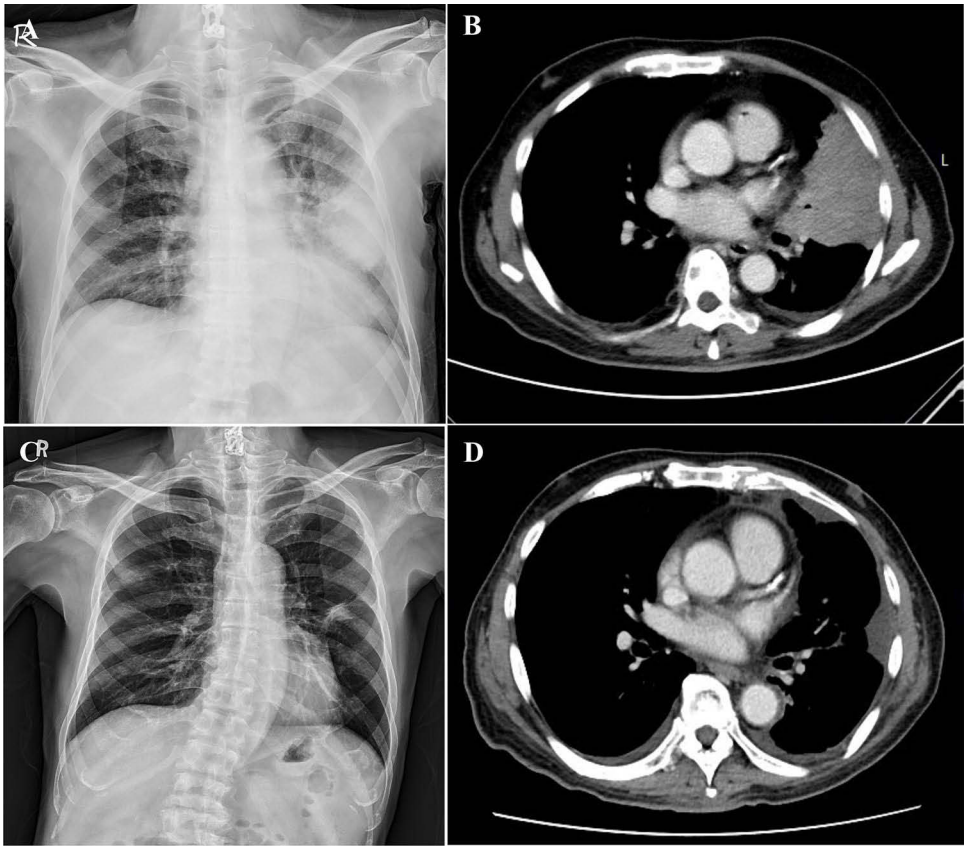

Figure 1 Radiographic findings before and after dacomitinib treatment. (**A**) Chest X-ray showed a mass-like opacity in the left lung field. (**B**) CT scan displayed a 7×7 cm mass in the left upper lobe, with enlarged contralateral mediastinal lymph nodes and evidence of multiple bony metastases. (**C**) Chest X-ray and (**D**) CT scan revealed a reduced lung tumor size in the left upper lobe after dacomitinib therapy.

upper lobe with contralateral mediastinal lymph nodes enlargement, and multiple bone metastases (Figure 1B). Brain magnetic resonance imaging (MRI) showed a 2.2×1.6 x 1.5 cm lesion with mixed signal intensity in the left thalamus indicative of a metastatic lesion with associated hemorrhage (Figure 2A). Moreover, multiple nodular metastases were identified in the left cerebral hemisphere, along with a metastatic lesion in the left parietal bone. A lung tumor biopsy showed a poorly differentiated lung adenocarcinoma with *EGFR* Ex21 L858R mutation. The patient was diagnosed with stage IVB (T4N3M1c) lung adenocarcinoma, characterized by mediastinal lymphadenopathy and metastases to the brain and multiple bones.

He started treatment with dacomitinib at a daily dosage of 45 mg. After a 6-month course of treatment, both chest X-ray (CXR) and CT scans demonstrated a significant reduction in the lung lesions (Figure 1C and D). Additionally, the brain MRI showed a complete response in the brain metastases (Figure 2B). During monthly evaluations, the patient reported side effects like acneiform eruption, paronychia, and lower limb edema caused by dacomitinib therapy. Consequently, the dosage was progressively reduced from 45 mg to 30 mg, and finally to 15 mg over a period of 5 months. Nevertheless, after 10 months of therapy, the disease progression was observed. CXR and CT scans showed an increase in the size of the primary lung tumor and newly developed pleural nodules with moderate effusion (Figure 3A and B). The brain MRI revealed no interval change in the brain lesion. Next-generation sequencing (NGS) analysis of the pleural fluid revealed the presence of *EGFR* L858R mutations with an allele frequency of 19.5% and a *CCDC6-RET* fusion (Figure 4 and Table S1).

Second-line oral vinorelbine was initiated, but refractory pleural effusion persisted. Third-line chemotherapy with cisplatin, pemetrexed, and bevacizumab was prescribed, followed by maintenance therapy of pemetrexed and bevacizumab, which effectively reduced tumor size and effusion (Figure 3C and D). However, the patient experienced worsened lower limb weakness and decreased consciousness after a 6-month course of treatment. The brain CT scan showed hydrocephalus without apparent metastatic lesions (Figure 5A and B). Additionally, while a diagnostic lumbar puncture

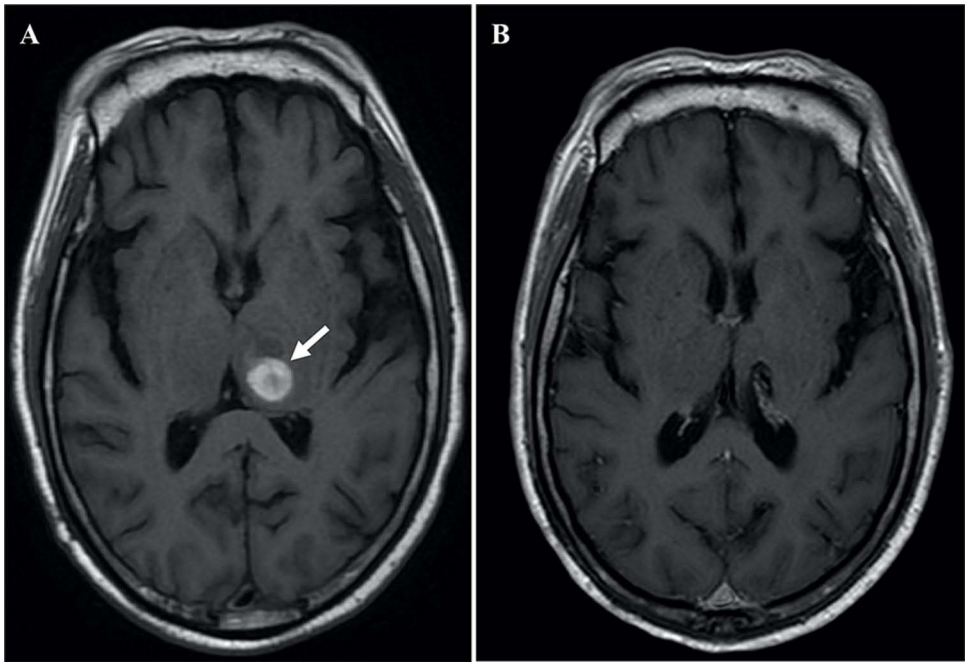

Figure 2 MRI scans displayed a metastatic lesion in the left thalamus before and after dacomitinib treatment. (**A**) Axial MRI scan showed a 2.2×1.6 x 1.5 cm lesion with mixed signal intensity (arrow), suggestive of a hemorrhagic metastatic lesion. (**B**) Axial MRI scan revealed complete remission of the previously noted metastatic lesion.

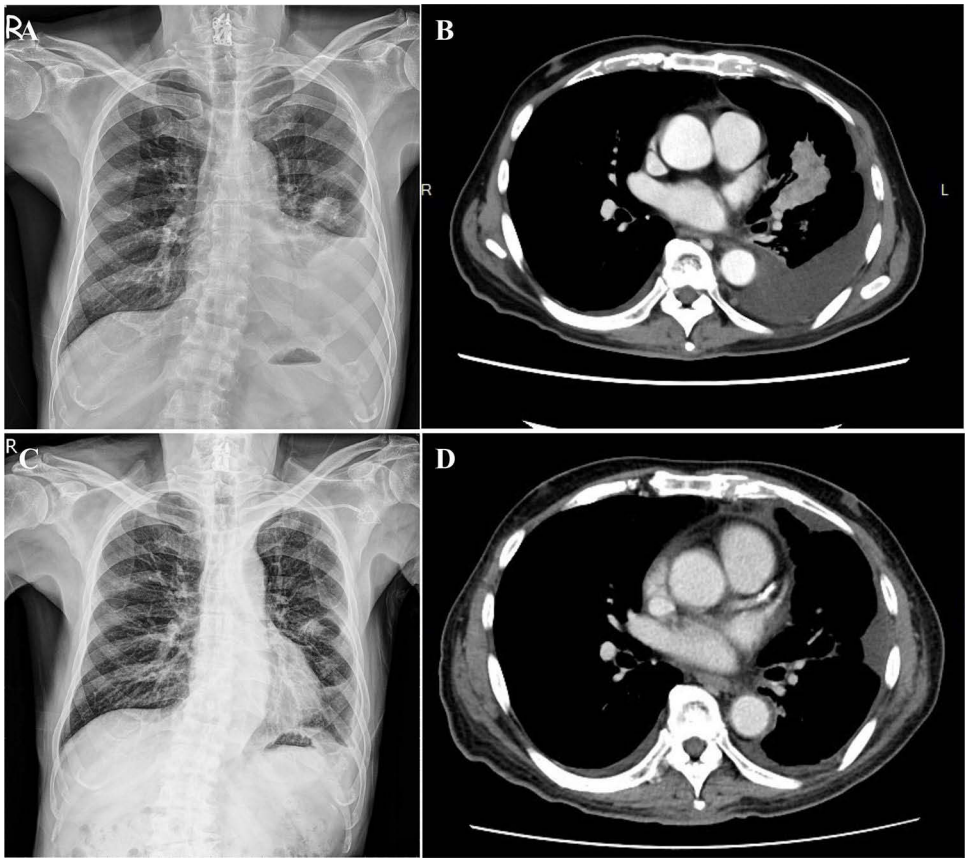

Figure 3 Radiographic findings before and after chemotherapy treatment. (**A**) Chest X-ray and (**B**) CT scan demonstrated an enlarged primary lesion in the left upper lobe with associated pleural effusion. (**C**) Chest X-ray and (**D**) CT scan revealed a decreased size of the tumor in the left upper lobe with diminished pleural effusion after chemotherapy.

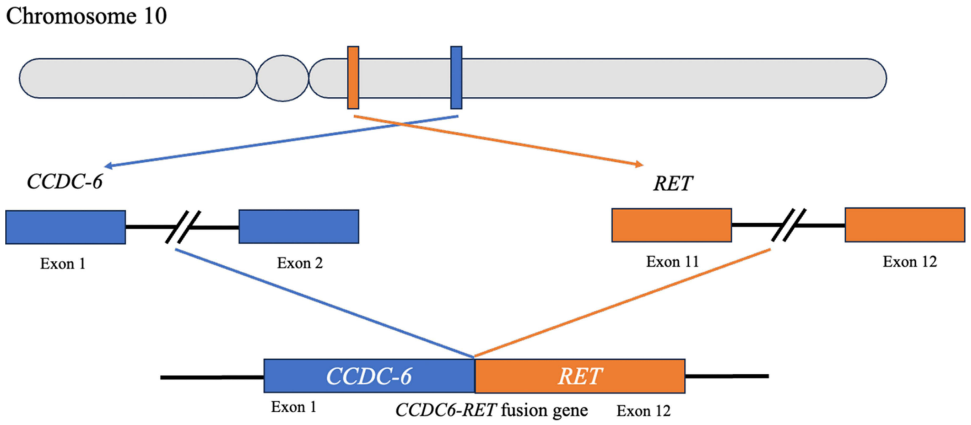

Figure 4 Diagram of the *CCDC6-RET* fusion gene on chromosome 10. The schematic illustrates the fusion between exon 1 of the *CCDC6* gene and exon 12 of the *RET* gene, resulting in the *CCDC6-RET* fusion gene.

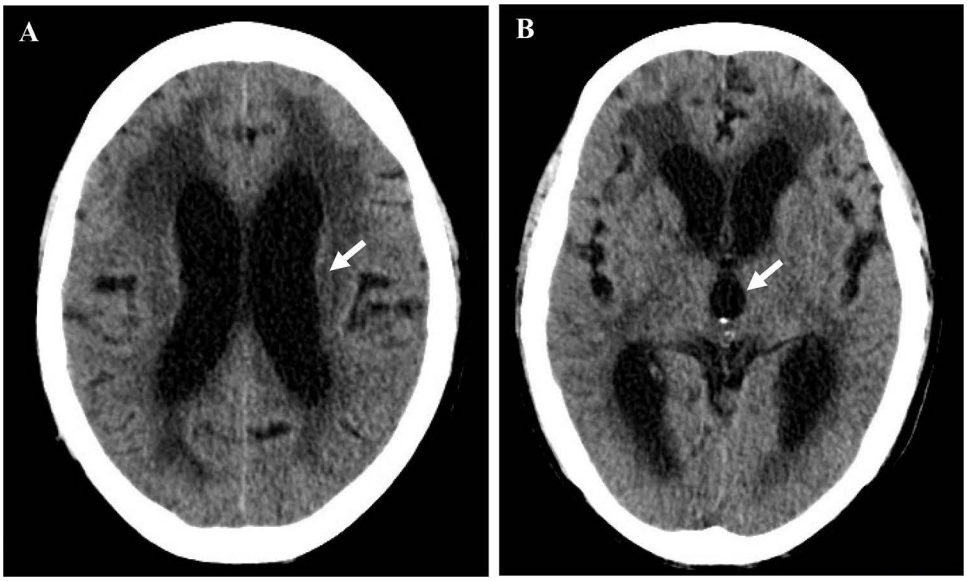

Figure 5 Brain CT scans depicting hydrocephalus. (**A**) Exhibited a dilated lateral ventricle (arrow). (**B**) Showed an expanded 3rd ventricle (arrow).

showed no malignant cells in the cerebrospinal fluid (CSF), the persistent elevation of CEA levels suggested ongoing disease progression. Fourth-line chemotherapy with docetaxel and ramucirumab was initiated but showed limited improvement. Consequently, the treatment strategy was changed to a combination of dacomitinib (30 mg daily) and the RET kinase inhibitor selpercatinib (80 mg daily). After a 1-month period of the combination treatment, there were notable improvements in consciousness and strength in both the upper and lower limbs (Figure 6A and B). His treatment timeline and response are shown in Figure S1.

Discussion

Recent studies have highlighted the significance of fusion genes as resistance mechanisms to EGFR inhibitors in *EGFR*-mutant NSCLC.[6–11] Although *RET* rearrangements and *EGFR* mutations are established as driver alterations in NSCLC, their simultaneous occurrence remains extremely rare. Acquired *RET* fusions, which emerge as resistance mechanisms, have been identified in *EGFR*-mutant NSCLC following EGFR- treatment. Kobayashi et al conducted a comprehensive

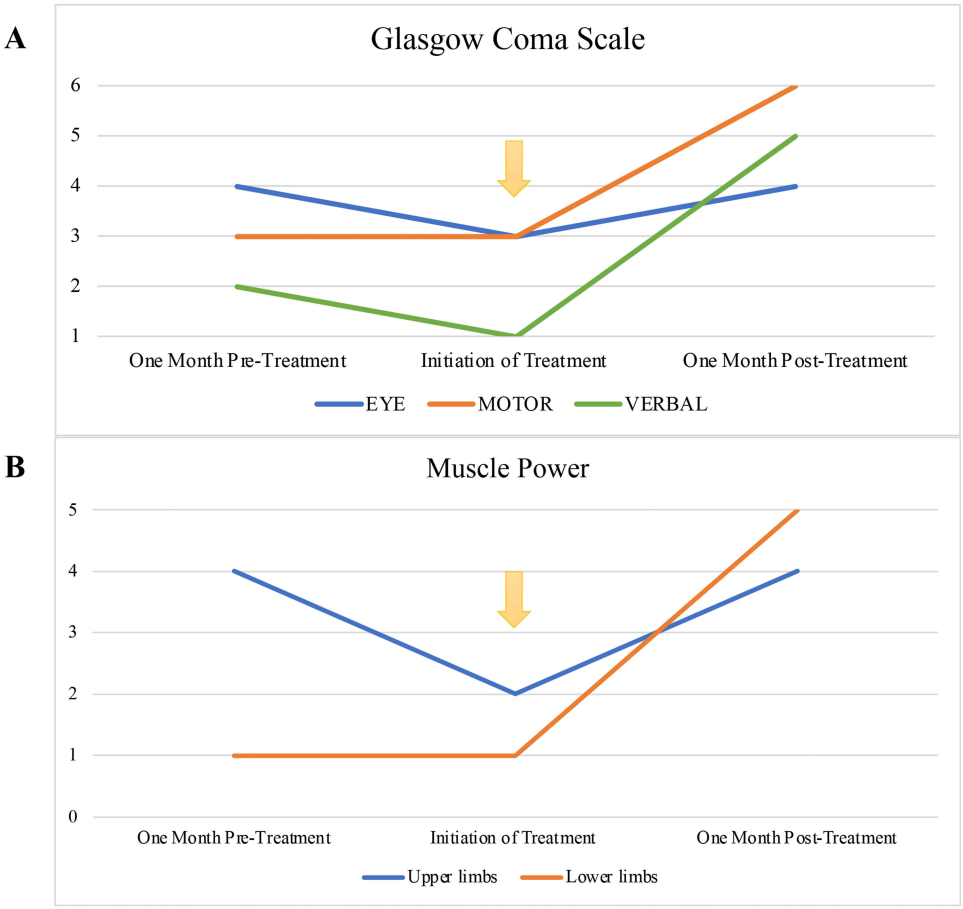

Figure 6 Clinical progression measured by Glasgow Coma Scale and muscle strength evaluation. (**A**) Displayed improvement in Eye, Motor, and Verbal responses as per the Glasgow Coma Scale. (**B**) Illustrated the increase in muscle power for both upper and lower limbs. The initiation of combined treatment is denoted by a yellow arrow.

study on fusion genes and their role in mediating resistance to EGFR TKIs in *EGFR*-mutant lung cancer.[12] Specifically, they identified that only a minority of detected fusion genes, such as *CCDC6-RET*, are functional and capable of imparting resistance to EGFR inhibitors. In a brief review, Zhao et al reported that the co-occurrence of *EGFR* mutations and *RET* fusions in patients with *EGFR*-mutant NSCLC is predominantly induced by osimertinib, a third-generation EGFR-TKI.[4] Furthermore, they observed that most *RET* fusions involved *CCDC6, NCOA4*, and *ANK3-RET*.[5] Nonetheless, data regarding acquired *RET* fusions induced by other EGFR-TKIs, particularly dacomitinib, and the combined treatment efficacy with RET inhibitors, remains limited. In this report, we present the first case of *CCDC6-RET* fusion induced by first-line dacomitinib treatment and reveal a promising treatment response in combination with RET inhibitor selpercatinib.

Multiple methods have been utilized for *RET* analysis, including Next-Generation Sequencing (NGS), Fluorescence In Situ Hybridization (FISH), immunohistochemistry, and Reverse Transcription Polymerase Chain Reaction (RT-PCR).[13] Currently, NGS is the most sensitive technique for detailed *RET* analysis, capable of identifying upstream gene partners and concurrent genomic aberrations that may predict treatment response.[14] DNA-based NGS detects genomic alterations but may miss gene fusions in low-quality samples, whereas RNA-based NGS can identify overlooked *RET* fusions.[15] RT-PCR is effective for detecting the most common *RET* fusion partners but may not identify rarer ones. *RET* FISH offers 100% sensitivity but has only 45–60% specificity and 39–55% false positives; subsequent use after RT-PCR may reduce these false positives.[16] Meanwhile, RET immunohistochemistry offers limited clinical utility due to its relatively low sensitivity and specificity. As there are no distinctive clinical characteristics for this NSCLC subset, it's recommended to perform *RET* analysis on both newly diagnosed cases and those showing resistance to EGFR-TKI treatment to detect both *de novo* and acquired *RET* fusions.

Dacomitinib is distinguished as the only EGFR TKI that has demonstrated both PFS and OS benefits over first-generation EGFR TKI specifically in NSCLC patients harboring the *EGFR* L858R mutation, as demonstrated in the ARCHER 1050 study,[1,2] in comparison to afatinib[17,18] and osimertinib.[19,20] Consistently, in vitro studies have shown that dacomitinib exhibits the lowest IC50 in lung cancer cell lines with the *EGFR* L858R mutation, surpassing other EGFR TKIs, including osimertinib.[21] These critical insights form the cornerstone of our treatment rationale, offering a solid foundation for our therapeutic strategy. Additionally, while dacomitinib has demonstrated significant survival outcomes over gefitinib, its effectiveness on the central nervous system (CNS) remains uncertain as the ARCHER 1050 study excluded patients with brain metastases.[1] A recent case series study indicated that dacomitinib has potent efficacy for central nervous system (CNS) metastasis in *EGFR*-positive NSCLC, with an intracranial metastases response rate of 85.7%.[22,23] In consistent with these results, our case achieved complete remission of brain metastases following a 6-month dacomitinib treatment, underscoring its potent efficacy in managing CNS metastases in *EGFR*-mutant NSCLC.

Selpercatinib and pralsetinib are commercially available RET inhibitors for treating *RET* fusion in NSCLC patients. However, the combination of EGFR-TKIs and RET inhibitors lacks clinical research to determine effective and minimally toxic dosage guidelines. Recent case series have revealed that combining osimertinib and selpercatinib is feasible, safe, and beneficial for patients with *EGFR*-mutant NSCLC harboring an acquired *RET* fusion.[24] Furthermore, a few case reports have also confirmed the efficacy of an osimertinib and pralsetinib regimen.[4,5] However, these crucial clinical insights are predominantly based on data related to the EGFR-TKI osimertinib. Our case provides valuable evidence that the dosage and combination therapy of dacomitinib and selpercatinib is practical, safe, and favorable for patients with concurrent *EGFR* mutations and *RET* fusions. The dose of selpercatinib (80 mg daily) was chosen due to the patient's previous side effects from dacomitinib and the lack of established guidelines for their combined use. The patient experienced significant side effects, such as acneiform eruption, paronychia, and lower limb edema, on the full dose of dacomitinib, leading to a reduction from 45 mg to 30 mg, and eventually to 15 mg. Consequently, we began the combination treatment at 30 mg dacomitinib and 80 mg selpercatinib daily to ensure safety and tolerability without serious adverse events. This approach aligns with findings from the LIBRETTO-431 and ARCHER 1050 studies, which supported dose adjustments to manage side effects without compromising efficacy.[25,26] Notably, the patient sustained progressive disease with hydrocephalus, but no tumor cells were found in the cerebrospinal fluid (CSF), and there were no brain metastases or leptomeningeal carcinomatosis on the brain imaging studies. This condition may be explained by paraneoplastic syndromes or inflammatory responses, which can result in hydrocephalus without the presence of detectable tumor cells or metastases.[27,28] Furthermore, the improved neurological function observed highlights the significant CNS activity of both dacomitinib and selpercatinib. Such findings are especially relevant for contexts where the latest third-generation treatments may not be accessible due to economic constraints or regulatory reasons. For instance, the choice of dacomitinib over osimertinib was carefully considered based on its availability and the reimbursement policies in specific regions, providing vital data for similar clinical scenarios globally.

Several retrospective studies have indicated that pemetrexed-based regimens offer long-term survival benefits and are more effective than other chemotherapy regimens for patients with *RET*-rearranged NSCLC.[29,30] However, these studies primarily involved patients with *de novo RET* fusions. Consequently, the efficacy of pemetrexed-based regimens for individuals with acquired *RET* fusions and concurrent *EGFR* mutations remains uncertain. Our case initially received chemotherapy with cisplatin/pemetrexed/bevacizumab due to unavailable RET inhibitors and demonstrated favorable clinical responses. These findings suggest that the potential effectiveness of pemetrexed-based regimens for both *de novo* and acquired *RET* fusions.

Conclusions

To our knowledge, we report the first case of a *CCDC6-RET* fusion induced by first-line dacomitinib in a patient with an *EGFR* L858R mutation and progressive disease with hydrocephalus, which was safely and effectively treated with a combination of dacomitinib and selpercatinib. Additionally, NGS has proven to be instrumental in identifying *RET* fusions. For NSCLC patients with *EGFR* mutations and acquired *RET* fusion, pemetrexed-based chemotherapy presents a feasible alternative treatment when RET inhibitors are inaccessible.

Data Sharing Statement

All data related to the study are included in the paper.

Ethics Approval

This study was approved by the Institutional Review Board of the Tri-Service General Hospital for the publication of case details.

Informed Consent Statement

Written informed consent has been obtained from the patient to publish this paper.

Acknowledgment

The authors are grateful to the patient for his participation. An abstract of this paper was presented at the TSPCCM 2023 Congress as a poster presentation with interim findings.

Author Contributions

All authors made significant contributions to the reported work, including conception, study design, execution, data acquisition, analysis, and interpretation. They participated in drafting, revising, or critically reviewing the article, gave final approval of the version to be published, agreed on the journal to which the article was submitted, and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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