ISSN 2639-8109 | Volume 14

Annals of Clinical and Medical Case Reports®

Case Report Open Access

Non-Small Cell Lung Cancer Patients with RET Fusion-Positive Complicated by Severe Pneumonia and Disseminated Intravascular Coagulation: A Case Report

Jinghua Cui*

Department of Pulmonary and Critical Care Medicine, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University. Guangzhou, Guangdong, 510080, China

***Corresponding Author:**
Jinghua Cui, Department of Pulmonary and Critical Care Medicine, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University. Guangzhou, Guangdong, 510080, China

Received: 30 Mar 2025

Accepted: 06 Apr 2025

Published: 10 Apr 2025

J Short Name: ACMCR

Keywords: RET Fusion-Positive;Severe Pneumonia;Disseminated Intravascular Coagulation (DIC);Non-Small Cell Lung Cancer (NSCLC)

Citation: J Cui. Non-Small Cell Lung Cancer Patients with RET Fusion-Positive Complicated by Severe Pneumonia and Disseminated Intravascular Coagulation: A Case Report. Anna Clin Med Case Rep®. 2025; 14(11): 1-3

1. Abstract

Rearranged during Transfection (RET) inhibitor-associated pneumonia is a relatively rare adverse reaction. Disseminated intravascular coagulation (DIC) is an uncommon complication in advanced solid tumors, with research indicating that DIC is associated with adenocarcinoma histology, and as high as 20 - 60% of lung adenocarcinomas may harbor actionable mutations. To date, there have been no reported cases of DIC complicating RET fusion-positive non-small cell lung cancer (NSCLC). Herein, we present a case of a female patient with RET fusion-positive lung adenocarcinoma. She developed Pneumocystis jirovecii pneumonia within less than four months of treatment with pralsetinib 100mg qd for her tumor. Following anti-infective therapy, the pneumonia was controlled, and pralsetinib was dose-reduced to 80mg qd. Subsequently, she experienced extensive metastatic progression along with DIC accompanied by thrombocytopenia. Despite supplementation with clotting factors and platelet-raising treatments, the patient's coagulation function did not improve. As a salvage therapy, selpercatinib 80mg bid targeting RET was administered for 15 days, after which the patient succumbed to disease progression.

2. Introduction

RET gene rearrangements occur in approximately 1% to 2% of NSCLC [1] 98% of RET fusion-positive NSCLC cases are adenocarcinomas and about 70% of these patients present at stage IV at diagnosis [2,3].Suggesting that NSCLC patients with RET gene rearrangements may have a poorer prognosis and are more prone to distant metastasis.The most common RET fusions in lung cancer are KIF5B-RET (70% to 90%) and CCDC6-RET (10% to 25%), followed by NCOA4-RET, TRIM33-RET, ZNF477P-RET, ERCC1-RET, HTR4-RET, and CLIP1-RET (18%) [4-6]. Targeted RET inhibitors have significantly improved the survival of RET fusion-positive NSCLC patients, but treatment-related adverse reactions may arise, impacting the efficacy of anti-tumor therapy. Prior research has shown that pralsetinib, a novel small molecule kinase inhibitor, exhibits high potency and selectivity against wild-type RET, oncogenic RET fusions (including the most common KIF5B-RET and CCDC6-RET), as well as mutations such as RET V804L, RET V804M, and RET M918T. However, its efficacy against rare driver proteins like LIMCH1-RET remains uncertain. In most cases, infections develop within 6 months of pralsetinib use, with a median time to pneumonia onset of 2.15 months (range 1.1 to 6.63) [7]. While most patients' infections improve, allowing for either resumption or dose reduction of pralsetinib to continue benefiting from the treatment, the impact on survival and prognosis is not yet clear.DIC is a rare complication in advanced malignancies, and DIC in conjunction with ALK, ROS1, and EGFR mutated non-small cell carcinomas has been reported, but there have been no reports of DIC in RET fusion-positive NSCLC. Compared to patients with ALK rearrangements, EGFR receptor mutations, and ROS-1 fusions, RET fusion-positive NSCLC patients typically exhibit poorer tumor cell differentiation [8]. Past literature suggests that targeted therapy can be effective in both DIC with and without thrombocytopenia in NSCLC cases presenting with DIC, potentially prolonging survival in these patients.9 Nevertheless, the potential benefits of targeted therapy for RET fusion-positive advanced NSCLC patients with poor performance status, concurrent DIC and widespread metastases remain unknown. Here, we report a case of a female patient with RET fusion-positive lung adenocarcinoma who sequentially developed severe pneumonia and DIC.

3. Case Presentation

A 43-year-old Chinese female presented to our center due to recurrent cough with white phlegm for over a month and blood-streaked sputum for ten days. Her medical history included hepatic S3/2A hemangioma for over 2 years and chronic hepatitis B virus (HBV) for more than 20 years, for which she has been receiving anti-virus therapy. Positron emission tomography/computed tomography (PET-CT) in February 2023 showed a soft tissue mass shadow (29*27mm) at the right lower pulmonary hilum, poorly defined margins, lobulated appearance and spiculation signs. Additionally, lymph node shadows were observed in the right hilar region and mediastinum and right supraclavicular. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from the right lower lobe mass suggested non-small cell carcinoma. Immunohistochemistry (IHC) results supported the diagnosis of invasive adenocarcinoma of the lung and the expression of PD-L1 in tumor tissues was over 10%. The next-generation sequencing (NGS) test results indicated RET gene fusions: LIMCH1-RET (L1:R12), abundance 23.98% and RET gene: KIF5B-RET (K15:R12) abundance 6.6%. According to the 8th edition of the International Lung Cancer Staging System, she was confirmed stage IIIB (CT4N3M0) and her Eastern Cooperative Oncology Group performance status (ECOG PS) score was 1. Because of RET fusion-positive, she received targeted treatment with RET inhibitor, Pralsetinib 100mg qd. Upon a follow-up enhanced CT scan on April 14, 2023, a soft tissue shadow (25*20mm) was detected in the right lung, with the treatment response evaluated as stable disease (SD). Thus, the patient continued to receive Pralsetinib treatment.The patient was admitted to our center due to recurrent fever and cough for over half a month on June 11, 2023, who was diagnosed with severe pneumonia (systolic blood pressure was less than 90mmHg, arterial blood gas analysis indicated an oxygenation index below 300mmHg

and a contrast-enhanced pulmonary CT scan showed diffuse ground-glass opacity lesions in both lungs). After bronchoscopic alveolar lavage fluid (BALF) NGS detection suggested Pneumocystis jiroveci. Therefore, we gave the anti-infective treatment plan to compound sulfamethoxazole tablets (960mg q6h), caspofungin (first 70mg qd, and then changing 50mg qd), piperacillin sodium tazobactam sodium (4.5g q8h) and methylprednisolone 40mg qd, the patient's symptoms improved. However, she developed a generalized rash on June 23rd, which was highly suspected to be a drug eruption. Consequently, we stopped compound sulfamethoxazole tablets and piperacillin sodium tazobactam sodium, and she was given loratadine 10mg orally, Dexamethasone 5mg and Calcium Gluconate 1g qd for antiallergic therapy. As the patient's Pneumocystis jirovecii pneumonia treatment course was incomplete, clindamycin palmitate granules (150mg tid) were added orally on June 26th, along with diphenhydramine tablets (25mg bid) as an antiallergic treatment. She was discharged on June 28th and continued oral administration of Clindamycin Palmitate Granules during this period. Meanwhile, Pralsetinib was temporarily discontinued during the infectious episode after multidisciplinary team discussions, and the possibility that it might have been related to the Pneumocystis jirovecii infection could not be ruled out. Given that the patient was not in an immunosuppressed state, Pralsetinib could be resumed but reduced to a dosage of 80mg qd.PET/CT scan in August 2023 comparing to the PET/CT from February 23rd: the primary mass near the hilum of the right lower lobe had slightly increased in size to 28X35mm, multiple new metastatic lesions were found in the liver, right pleura, multiple bones, regional and peritoneal lymph nodes, as well as retroperitoneal lymph nodes. Right-sided pleural effusion and pelvic effusion was also observed. Biopsy of the left supraclavicular lymph node revealed adenocarcinoma metastasis, consistent with pulmonary origin. Cytological sediment from right pleural effusion showed carcinoma cells. She was confirmed stage IVB (T4N3M1c) with a progressive disease (PD) response evaluation and PD-L1 (22C3) expression was approximately 60%. Hence, a platinum-based doublet chemotherapy plus immunotherapy according to the clinical guidelines was administered starting from August 12th, 2023, consisting of Cisplatin (743mg) + Pemetrexed (653mg) + Bevacizumab (375mg) + Sintilimab (200mg). After the treatment, she experienced grade IV neutropenia accompanied by fever, grade IV thrombocytopenia and grade III skin rash. Symptomatic treatments including leukocyte and platelet boosting, platelet transfusion, methylprednisolone 80mg, and pleural effusion drainage led to improvement. Due to these adverse events, we eliminated carboplatin in the second cycle of treatment and reduced pemetrexed to 80%. CT evaluation after cycle 2 showed stable disease (SD), with improvement absorption of the pleural and abdominal effusions. However, because the patient experienced symptoms such as sore throat and runny nose, cycle 3 chemotherapy was not carried out at that time.The patient was re-admitted to the hospital thanks to fever for 10 days on October 29, 2023. Enhanced CT of the chest and whole abdomen scan indicated that it was consistent with right lung cancer with multiple organ metastases, which were roughly similar from before. Multiple metastases in the liver that were significantly larger and more numerous than before. Her pathology results noted white blood cell 29.92*10^9/L, platelet 38*10^9/L, D-dimer 8720 ng/mL, plasma fibrinogen level 0.76 g/L, prothrombin activity 61%, prothrombin time (PT) 17.2 s and activated partial thromboplastin time (APTT) 47.7 s. The diagnosis was confirmed as stage IVB (T4N3M1c) and her response evaluation was progressive disease (PD). She was treated with imipenem cilastatin sodium for anti-infection. Combined with chest and whole abdomen enhanced CT examination, the lung lesion was stable and the liver lesion was enlarged obviously. Considering the possibility of pneumonia combined with tumor fever, we added celecoxib (200mg bid) and her temperature was well under control.Since November 4, D-dimer had continued to rise (>20000 ng/mL) and plasma fibrinogen had continued to fall (<0.6 g/L), and there was active bleeding from the nose, scattered small bleeding spots on the skin, she was diagnosed with DIC according to the International DIC Scoring System for Diagnosis. With abnormal coagulation function and bleeding tendency, she was not anticoagulated for the time and treated with transfusion of human fibrinogen, fresh frozen plasma and platelet-boosting therapy. However, the condition keeps getting worse. In view of the patient's poor PS score, she could not be enrolled in clinical trials, coagulation abnormalities because of tumor progression. There were existing contraindications in the current relevant chemotherapy and immunotherapy, but the patient's willingness to treatment was active. According to the clinical guidelines and expert consensus, Selpercatinib (80mg bid)was administered for anti-tumor treatment on November 6th, which continued for 15 days. Unfortunately, the patient passed away on November 21st, with an overall survival time of 9 months.

4. Discussion

The concurrent occurrence of severe pneumonia and DIC in RET fusion-positive NSCLC is highly unusual, especially there have been no reported cases of DIC in conjunction with RET fusion-positive NSCLC. In the present case, the patient developed Pneumocystis jirovecii pneumonia less than four months after initiating first-line treatment with pralsetinib. The medication was discontinued following anti-infection therapy which improved her condition. After our team's deliberation, it was considered that Pneumocystis jirovecii pneumonia might be related to pralsetinib use, despite the absence of an immunosuppressed state in the patient, a reduced dosage of pralsetinib was resumed for continued anti-tumor treatment.The latest results from the ARROW study show that pralsetinib in previously untreated advanced RET fusion-positive NSCLC patients (n=75), the ORR was 72%, while in those who had received prior platinum-based chemotherapy (n=136), the ORR was 59%. Median PFS was 13.0 and 16.5 months, respectively.10 A study on pralsetinib-related pneumonia in RET fusion-positive NSCLC7 defined it as pneumonia with radiological and microbiological evidence following pralsetinib treatment, excluding pneumonia caused by other clear infections, immune checkpoint inhibitor-associated pneumonia, radiation pneumonitis, or interstitial pneumonia. Pralsetinib-related pneumonia is a rare adverse event, occurring in approximately 15% of cases. In this literature, eight cases of pneumonia after pralsetinib treatment were analyzed. All were adenocarcinomas, predominantly female and non-smokers. Fusion genes included KIF5B (87.5%) and KIAA1468 (12.5%). All patients suffered from opportunistic infections, with Human Herpesvirus and Pneumocystis jirovecii being the most common pathogens. 1 patient died due to disease progression, while 7 patients restarted pralsetinib after infection control and continued to benefit, with a median follow-up time of 17.4 months and an unreached median PFS.The case we report presents with both radiological and microbiological evidence consistent with pralsetinib-related pneumonia, suggesting that it may also represent pralsetinib-related pneumonia. Analogous to the above-mentioned research, the first-line PFS in this case was 5 months and not reached the median PFS, indicating a disparity with the reported data, suggesting that pralsetinib-related pneumonia might impact the survival and prognosis of RET fusion-positive NSCLC. Unlike the others, this patient primarily harbored the LIMCH1 fusion gene (abundance 23.98%), followed by KIF5B (abundance 6.6%). Progression occurred within two months of continuing pralsetinib use. We observed that patients with KIF5B as the primary fusion gene did not progress until more than 20 weeks after pralsetinib resumption following improvement in pneumonia [7]. We speculate that the difference in RET fusion gene type and abundance might be related to this outcome, suggesting that pralsetinib's efficacy against rare driver proteins such as LIMCH1 might be inferior to that against common drivers like KIF5B and CCDC6. Moreover, NSCLC cases with rare RET driver proteins might have a poorer prognosis. This could potentially explain the rapid progression after a short-term re-administration of pralsetinib following improvement in pneumonia.Kanaji N et al. [9].Evaluated 716 pathologically confirmed lung cancer patients and reported an

overall prevalence of DIC at only 0.7%, rising to 1.5% in stage IV disease.11 There have been no documented cases of RET fusion-positive NSCLC complicated by DIC so far. We report this case of a female patient with poor PS score, concurrent DIC, and advanced metastatic lung adenocarcinoma who experienced progression after first-line treatment with pralsetinib and second-line platinum-based doublet chemotherapy combined with immunotherapy, subsequently receiving selpercatinib (80mg bid, at a reduced dose due to her poor PS and related contraindications) for 15 days before succumbing to tumor progression. This differs from previous studies. Justin L. Pevner and colleagues [9].Reviewed 17 cases of NSCLC with DIC that received targeted therapy between 2013 and 2022 in the PubMed database, including those with EGFR, ALK, ROS1, and ERBB2 mutations, indicating that targeted therapy is effective for DIC with or without thrombocytopenia and may extend survival in these patients. The latest data from the LIBRETTO-001 study (selpercatinib) showed that among 247 previously treated advanced RET fusion-positive NSCLC patients, the ORR was 61.1% with a median PFS of 24.9 months. In 69 treatment-naive patients, the ORR was 84.1% with a median PFS of 22 months [12]. However, unlike NSCLCs with other target mutations, this RET fusion-positive extensively metastatic NSCLC patient with DIC and thrombocytopenia did not achieve an ideal survival outcome following targeted therapy, nor did it reach the median PFS observed with selpercatinib in previously platinum-treated advanced patients. This suggests that targeted therapy might confer limited benefits for advanced RET fusion-positive NSCLC patients with thrombocytopenic DIC.Existing research indicates that coagulation dysfunction may be associated with the occurrence, development, clinical treatment, and prognosis of malignant tumors [13,14]. Persistent elevation of D-dimer often suggests disease progression or a poor prognosis [15]. A study examining the clinical characteristics of lung cancer patients with thromboembolism or disseminated intravascular coagulation16 found that in 25 cases with thromboembolism and 21 cases with DIC, the median survival time after the onset of thromboembolism was 223 days, significantly longer than the survival time after DIC onset (13 days). Cox proportional hazards model multivariate analysis identified older age, poor PS, multiple metastatic organs, lack of EGFR mutations/ALK fusions, presence of interstitial lung disease (ILD), and DIC as adverse prognostic factors for OS in lung cancer patients with thromboembolism or DIC. This implies that patients with RET fusion-positive, extensively metastatic late-stage lung cancer and DIC, especially those with poor PS, may have shorter survival times and worse prognoses, necessitating exploration of effective treatment strategies.

A limitation of our report is that we did not perform a bone marrow biopsy to further clarify whether DIC was caused by tumor invasion or hematological disorders. Moreover, due to the small number of cases and considering the patient's poor PS leading to the use of reduced doses of targeted drugs, it cannot be definitively concluded that advanced, widely metastatic RET fusion-positive NSCLC patients with DIC and thrombocytopenia could not benefit from targeted therapy.

5. Conclusion

In summary, we present a case of RET fusion-positive lung adenocarcinoma complicated by pralsetinib-associated pneumonia and disseminated intravascular coagulation. The pralsetinib-related pneumonia can be improved with anti-infection treatment. However, it may negatively impact the patient's survival and prognosis. NSCLC patients with rare RET driver proteins appear to have a worse prognosis. Multi-line progression in advanced RET fusion-positive NSCLC patients complicated by DIC may derive limited benefit from targeted therapy, potentially resulting in shorter survival times and poorer prognoses. Due to the limited number of cases, these findings require further validation through extensive research.

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