Case Report

Use of on-therapy ctDNA monitoring in a patient with *KIF5B-RET* fusion positive advanced non-small cell lung cancer: a case report

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Abstract: Molecular characterization of non-small cell lung cancer (NSCLC) has led to marked improvements in the treatment of patients with advanced disease who harbor driver mutations, including those with alterations in the *RET* proto-oncogene. Liquid biopsy to detect circulating tumor DNA (ctDNA) is a clinically validated tool to identify genomic alterations in advanced NSCLC at diagnosis and disease progression. Whether ctDNA assessment can be integrated into other aspects of patient care is an area of ongoing active research. Here, we present the case of a 65-year-old female with *KIF5B-RET* fusion-positive advanced NSCLC who underwent on-therapy ctDNA surveillance while being treated on a phase 1b trial with the oral RET inhibitor RXDX-105. The patient initially presented with right-sided flank discomfort, with a CT scan identifying a large right lower lobe (RLL) lung mass and right-sided pleural effusion. CT-guided biopsy confirmed thyroid transcription factor 1 (TTF-1) positive lung adenocarcinoma. Subsequent video-assisted thoracoscopic surgery to assess resectability identified pleural studding, with pleural biopsy confirming advanced unresectable disease. Next-generation sequencing (NGS) of tumor tissue and peripheral blood confirmed the presence of a *KIF5B-RET* fusion, prompting initiation of trial therapy RXDX-105. After 1 year on therapy, ctDNA became detectable prompting early scans which identified disease progression. The patient was subsequently enrolled onto a phase II trial of the RET inhibitor pralsetinib, on which she continues to this day (2+ years) without detectable *KIF5B-RET* ctDNA and with an ongoing minor response [stable disease per response evaluation criteria in solid tumors (RECIST) v1.1] on imaging. This case illustrates a potential role for on-therapy ctDNA monitoring as a non-invasive method to evaluate treatment response and detect early relapse in patients with advanced NSCLC. Prospective investigation is required to clearly define the optimal integration of ctDNA testing into on-treatment surveillance in patients with advanced NSCLC.

Keywords: Circulating tumor DNA (ctDNA); liquid biopsy; RET; pralsetinib; non-small cell lung cancer (NSCLC); case report

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Introduction

In the last decade, the treatment paradigm for non-small cell lung cancer (NSCLC) has evolved to include targeted therapy for oncogenic driver mutation subsets, the list of which continues to expand. Approximately 1–2% of NSCLC patients harbor a fusion in the *RET* proto-oncogene, and based on phase II clinical trial data, the selective RET inhibitors pralsetinib and selpercatinib currently garner accelerated Food and Drug Administration (FDA) approval for the treatment of such patients (1,2).

Tumor genotyping to detect actionable driver alterations is now standard-of-care in advanced NSCLC. Although

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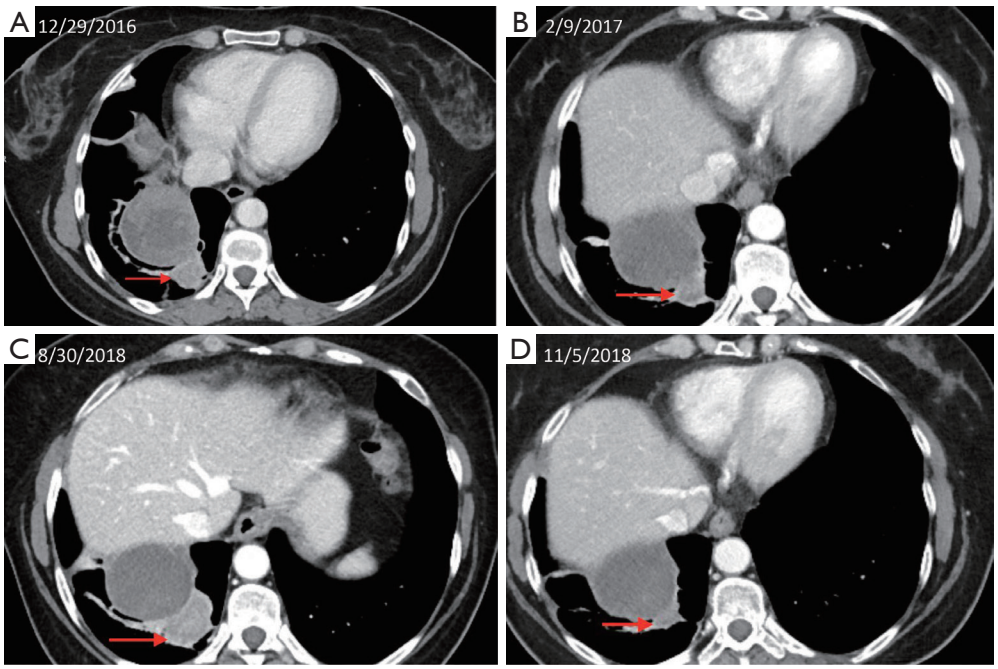

Figure 1 Imaging assessments during treatment. (A) CT of chest demonstrating RLL biopsy-confirmed *RET*-fusion positive NSCLC prior to RXDX-105 treatment initiation; (B) at follow-up on-treatment imaging assessment demonstrating stable disease with RXDX-105; (C) at progression of disease on RXDX-105; (D) and at follow-up on-treatment imaging assessment demonstrating stable disease with pralsetinib. Red arrow shows change in size of solid component of solid-cystic RLL mass. CT, computed tomography; RLL, right lower lobe; NSCLC, non-small cell lung cancer.

tissue molecular profiling has been the gold standard, there is an increasing role for non-invasive liquid biopsies that detect circulating tumor DNA (ctDNA) in peripheral blood. Up to 20% of NSCLC patients may be unable to provide a tumor sample suitable for molecular testing at diagnosis (3). In addition, liquid biopsies have several potential advantages over tissue biopsy including minimally invasive sampling, rapidity of testing and result reporting, decreased patient risk, and identification of additional therapeutic targets not identified on tissue testing (4-6). These advantages are magnified for patients harboring rare genomic alterations for whom enrollment onto clinical trials is critical. However, while ctDNA assessment is being increasingly integrated at diagnosis and at the time of acquired resistance to targeted therapy, its role in on-therapy surveillance remains to be defined.

Here we describe a patient with *KIF5B-RET* fusion-positive advanced NSCLC in whom on-treatment surveillance ctDNA monitoring was utilized, resulting in early, asymptomatic detection of disease progression on CT imaging. The patient was subsequently enrolled onto a clinical trial of pralsetinib, with ongoing response and no detectable ctDNA over 2 years following therapy change. We present the following case in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-571/rc).

Case presentation

A 65-year-old female with no significant past medical history initially presented to the emergency room in October 2016 with right-sided flank discomfort where a CT scan identified a right-sided pleural effusion and a 5.5 cm right lower lobe (RLL) lung mass (*Figure 1*). Positron emission tomography (PET) demonstrated a 6.0 cm × 7.7 cm fluorodeoxyglucose (FDG)-avid RLL lung mass with an FDG-avid 1 cm right paratracheal lymph node. A CT-guided biopsy of the RLL mass confirmed thyroid transcription factor 1 (TTF-1) + adenocarcinoma and next-generation sequencing (NGS) of tumor tissue revealed a *KIF5B-RET* fusion. Peripheral blood ctDNA testing (Guardant360, Foundation ACT) also identified a *KIF5B-*

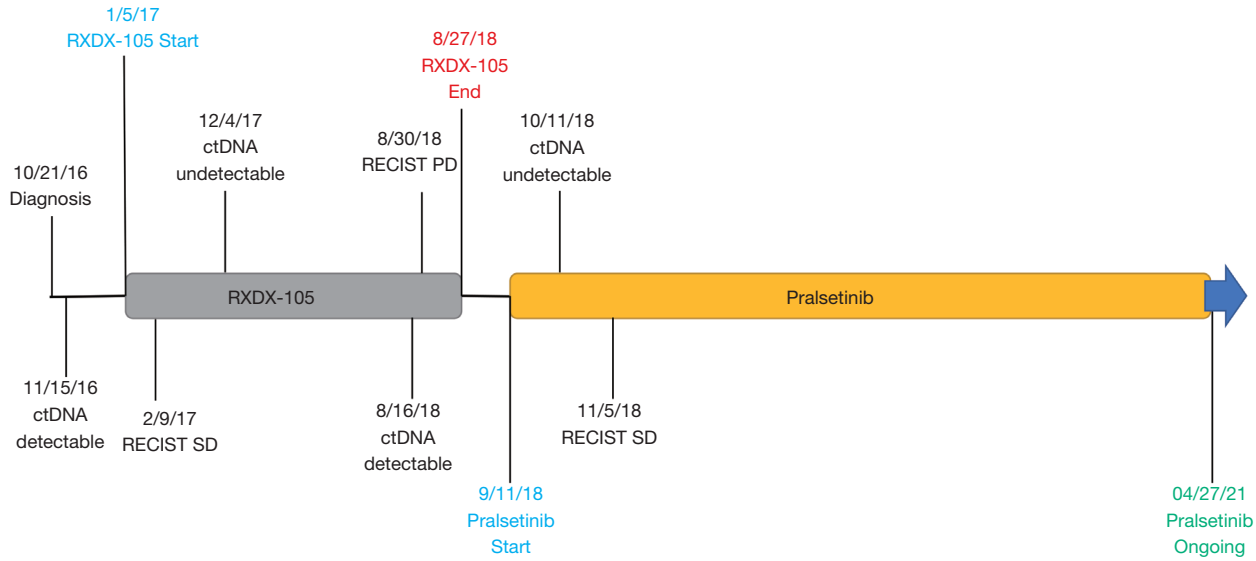

Figure 2 Timeline of clinical course. Timeline of patient's clinical course with key dates from diagnosis of biopsy-confirmed *RET*-fusion positive NSCLC up to and including most recent assessment on pralsetinib. At the time of submission of this report, the patient continues on pralsetinib 400 mg with ongoing imaging-assessed stable disease by RECIST v1.1 and undetectable *KIF5B-RET* ctDNA. Blue arrow indicates treatment is ongoing. ctDNA, circulating tumor DNA; RECIST, response evaluation criteria in solid tumors; PD, progressive disease; SD, stable disease; NSCLC, non-small cell lung cancer.

RET fusion [7.1% variant allele fraction (VAF)]. Brain MRI was negative for intracranial disease. In order to assess tumor resectability, video-assisted thoracoscopic surgery was performed, which identified pleural studding. Subsequent decortication and pleurodesis with pleural biopsy confirmed metastatic adenocarcinoma, with NGS (Foundation One) revealing the same *KIF5B-RET* fusion. At the time of diagnosis of metastatic disease, the patient was experiencing intermittent cough and back pain, but was otherwise asymptomatic. Physical exam was unremarkable with the exception of decreased breath sounds at the right lung base.

In January 2017, the patient was enrolled onto a phase Ib study of RXDX-105, an oral RET inhibitor, at 275 mg daily (7). A CT scan obtained 1 month after therapy initiation showed stable disease (*Figure 1*). Subsequent CT scans were obtained every 2 months per protocol. At the patient's request, ctDNA was monitored at periodic intervals using Guardant360 ctDNA testing, initially monthly for the first 3 months followed by every 3–4 months thereafter once disease stability was established (*Figures 2,3*). The *RET* fusion remained undetectable by ctDNA assessment in December 2017, approximately 11 months following therapy initiation. Treatment course was unremarkable with the exception of transient grade 3 transaminase elevation requiring a dose reduction to 200 mg. The patient's imaging studies continued to show stable disease with periodic ctDNA monitoring revealing no detectable *KIF5B-RET* fusion (*Figure 3*).

In August 2018, after ~1.5 years on RXDX-105 therapy, ctDNA assessment identified detectable *RET-KIF5B* fusion (0.3% VAF); no *KIF5B-RET* fusion molecules were reported, but presence of the inactivating reciprocal conformation was strongly suggestive of re-emergence of the activating fusion (*Figures 2,3*). She had no symptoms, but the finding prompted restaging imaging 1 month early which revealed tumor growth in the RLL to 3.4 cm × 2.1 cm from 3.1 cm × 1.7 cm 1 month prior, consistent with disease progression (*Figure 1*). RXDX-105 was subsequently discontinued and in September 2018 the patient was enrolled onto a phase I/II study of pralsetinib at 400 mg daily (*Figure 2*). After 1 month on pralsetinib therapy, ctDNA analysis no longer detected the *RET* fusion and repeat CT imaging after approximately 2 months on therapy showed a minor response [stable disease per response evaluation criteria in solid tumors (RECIST) v1.1] (*Figure 1*). She tolerated treatment well, with transient grade 1 lower extremity swelling and AST elevation requiring no dose alterations. At the time of this report, the patient continues treatment with undetectable *KIF5B-RET* ctDNA

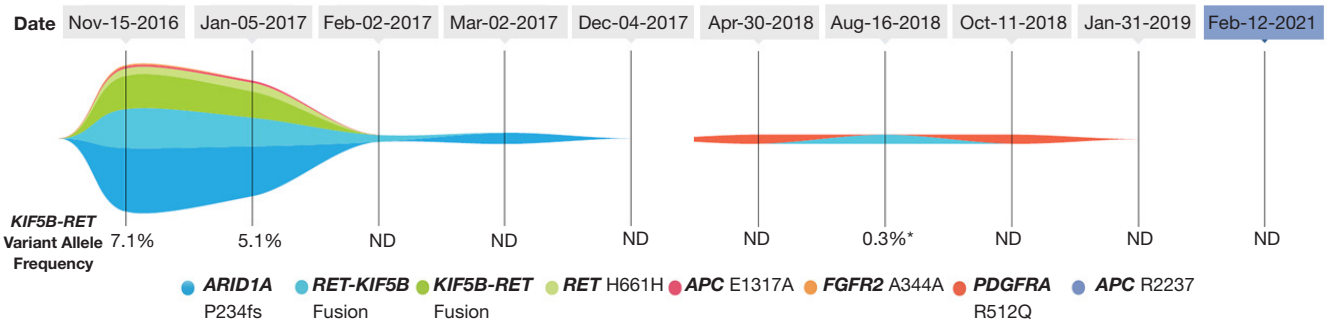

Figure 3 ctDNA surveillance. ctDNA assessment from diagnosis through most recent assessment on 2/12/21. ctDNA assessments made from 3/2/2017–12/4/17 and 1/31/19–2/12/21 revealed no detectable *KIF5B-RET* ctDNA and are not shown. *, no *KIF5B-RET* fusion molecules reported, but detection of the inactivating reciprocal *RET-KIF5B* conformation at VAF of 0.3% was strongly indicative of reemergence of the activating fusion and prompted early restaging imaging. ND, not detectable; ctDNA, circulating tumor DNA; VAF, variant allele frequency.

in plasma over 2 years after initiation of pralsetinib with an ongoing minor response (stable disease per RECIST v1.1) on imaging (*Figures 1-3*).

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 Helsinki Declaration (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

Although ctDNA analysis in advanced NSCLC has been well-established for identification of sensitizing mutations at diagnosis and resistance mutations at progression, on-therapy surveillance is a practical application that has yet to be defined. Here, we present a case where periodic on-treatment ctDNA surveillance in an asymptomatic patient with *RET*-fusion positive advanced NSCLC led to early identification of disease progression, resulting in expedited therapeutic decision-making.

There is a growing body of literature to support the use of ctDNA monitoring for early detection of disease progression in advanced NSCLC. In a sub-group analysis from the phase III FLAURA study, which randomized patients with advanced treatment-naïve *EGFR*-positive NSCLC to osimertinib or earlier generation tyrosine-kinase inhibitor, 122 patients underwent longitudinal ctDNA monitoring. Among these patients, ctDNA progression preceded or co-occurred in 66% of patients who had imaging-assessed disease progression, with a 2.7-month median lead-time (8). Similarly, in a prospective study of 100 patients with treatment-naïve advanced *EGFR*-mutant NSCLC who underwent serial ctDNA monitoring, increased on-treatment ctDNA was associated with disease progression (9). On-therapy ctDNA dynamics have also been shown to correlate with clinical outcomes in advanced NSCLC patients receiving immune checkpoint blockade (ICB). In a 24-patient study of ICB-treated patients with advanced NSCLC, increased ctDNA preceded imaging-assessed disease progression by an average of 8.7 weeks (10). A significant correlation has also been observed between synchronous changes in ctDNA levels and tumor size on imaging (11). In addition, early reduction in ctDNA following initiation of systemic therapy has been shown to be a predictive marker for clinical benefit in several other tumor types including advanced colorectal, bladder, and pancreatic cancer (12-14).

For this patient, ctDNA monitoring resulted in the early detection of disease progression in the absence of symptoms, which enabled a prompt change in therapy and enrollment onto a subsequent clinical trial, on which the patient continues to this day. One potential limitation of this report is that it is difficult to ascertain the true clinical benefit of this approach, as this strategy of on-treatment liquid biopsy for disease surveillance in a patient without symptoms may reflect lead-time bias. Furthermore, appropriate clinical decision-making that is informed by ctDNA recurrence is

an area that requires additional study. Several factors may affect subsequent patient management including clinical status, presence of driver mutation, presence of actionable mechanism of resistance, current therapy (targeted therapy *vs.* immunotherapy *vs.* chemotherapy), and additional therapeutic options (approved treatment *vs.* clinical trial). That said, the use of ctDNA monitoring for assessment of response and early detection of relapse in patients who are clinically asymptomatic could have particular utility for those with rare genomic alterations (such as the patient described in this report) for whom enrollment onto clinical trials, an often complex and time-consuming process, is critical. Randomized studies to evaluate the utility of ctDNA assessment in disease monitoring are ongoing in NSCLC, colorectal cancer and pancreatic cancer (NCT03334708, NCT03737539, NCT03664843, NCT03634826), though barriers to widespread implementation remain such as optimal interval of assessment and cost.

Conclusions

In conclusion, we present the case of a patient with *RET*-fusion positive advanced NSCLC in whom ctDNA surveillance prompted early imaging that resulted in expedited therapeutic decision-making. This report provides further evidence of the potential benefit of serial liquid biopsies during treatment as a useful, non-invasive method to evaluate treatment efficacy and detect relapse. Prospective investigation is needed to define the optimal integration of on-treatment ctDNA monitoring in patients with advanced NSCLC, and clarify the subsequent clinical decision-making that is informed by this testing.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-571/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-571/coif). CK reports serving as a consultant or advisory board member for Novartis, Janssen, Astrazeneca, Sanofi, PierianDx, and Diffuse pharmaceuticals. LAK reports employment with and shareholder of Guardant Health. SVL reports serving as a consultant or advisory board member for Amgen, AstraZeneca, Beigene, Blueprint Medicines, Bristol-Myers Squibb, Daiichi Sankyo, G1 Therapeutics, Genentech, Guardant Health, Inivata, Janssen, Jazz Pharmaceuticals, Lilly, Merck, PharmaMar, Pfizer, Regeneron and Takeda, and reports research funding (to institution) from Alkermes, AstraZeneca, Bayer, Blueprint Medicines, Bristol-Myers Squibb, Genentech, Lilly, Lycera, Merck, Merus, Pfizer, Rain Therapeutics, RAPT, Spectrum, and Turning Point Therapeutics. JER reports research funding (to institution) from Conquer Cancer Foundation of ASCO and reports serving as a consultant or advisory board member for Oncocyte. The other 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 Helsinki Declaration (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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