CASE REPORT

Spontaneous Bilateral Chylothorax Development During Alectinib Therapy for *ALK*-Rearranged NSCLC—A Case Report

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ABSTRACT

The emergence of spontaneous nonmalignant chylous effusions during treatment with various tyrosine kinase inhibitors (TKIs) has been previously described; however, there have been no prior reports for alectinib. Herein, we report a case of symptomatic bilateral chylothorax during alectinib therapy in a patient with *ALK*-rearranged lung adenocarcinoma. Although immediate control of symptoms was achieved by placement of bilateral tunneled pleural catheters, the chylothorax ultimately resolved only after alectinib discontinuation and transition to an alternative TKI. This case adds alectinib to the growing list of TKIs that may be associated with the rare emergence of spontaneous, nonmalignant chylous effusions.

Keywords: Lung adenocarcinoma; Alectinib; Chylothorax; Case report

Introduction

ALK gene fusions are well-studied oncogenes in NSCLC.[1] Later generation ALK tyrosine kinase inhibitors (TKIs), such as alectinib, are highly active as first-line treatments in *ALK*-rearranged NSCLC. Although these drugs have a manageable tolerability profile,[2] as the clinical experience with ALK TKIs expands, rare adverse events are increasingly recognized.

Our group previously described the emergence of spontaneous nonmalignant chylous effusions in patients treated with a wide variety of TKIs targeting the RET (rearranged during transfection) tyrosine kinase.[3] Although alectinib harbors anti-RET activity,[4] the emergence of chylous effusions during alectinib therapy has

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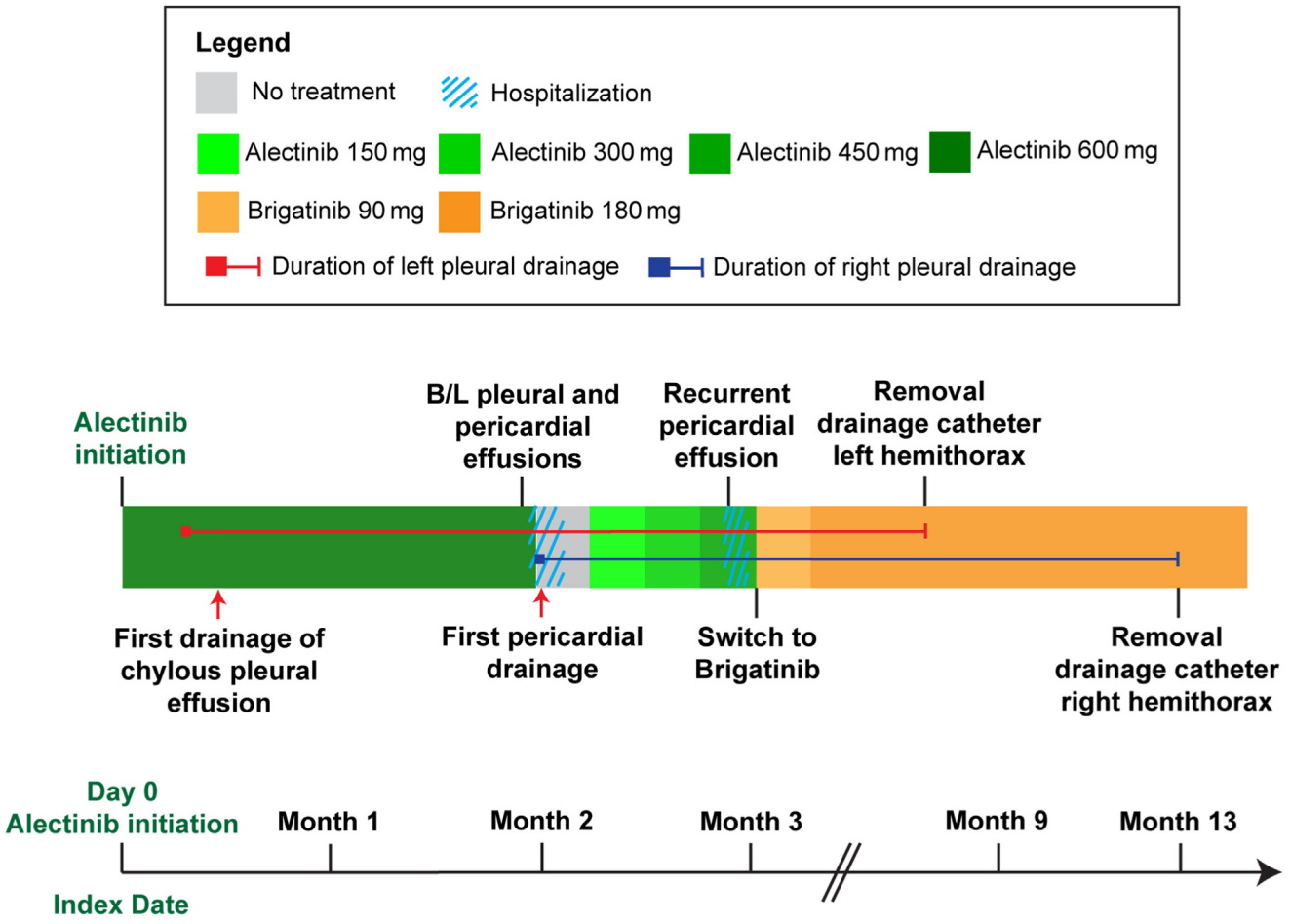

Figure 1. Clinical course timeline. The time course is indicated by the time bar at the bottom. The day of alectinib therapy initiation is labeled as the index date with post-index date pertinent events indicated over months.

not previously been described. Herein, we report the spontaneous emergence of bilateral nonmalignant chylothoraces in a patient with an *EML4-ALK*–rearranged lung adenocarcinoma on treatment with alectinib.

Case Presentation

A 30-year-old man, never smoker, presented with progressive subacute cough and cervical swelling for 1 month. Imaging revealed a right lung mass, mediastinal, supraclavicular, and axillary lymphadenopathy, a small right-sided pleural effusion, and a small pericardial effusion. Biopsy of an axillary lymph node revealed an *EML4-ALK*–rearranged lung adenocarcinoma (Supplementary Table 1).

First-line therapy with alectinib was initiated at the recommended full dose of 600 mg twice daily (Fig. 1). Eight days into alectinib therapy, the patient reported increasing dyspnea. Chest imaging revealed a decrease in the size of the primary lung mass and increased bilateral pleural effusions (Fig. 2*A* and *B*). The patient subsequently underwent placement of a left-sided tunneled pleural catheter and a right-sided thoracentesis (Fig. 1). Fluid from both pleural cavities was milky and grossly suggestive of a chylous effusion; however, triglyceride levels were not measured. Cytology result was negative for malignant cells in both fluid specimens. The decision was made to continue full-dose alectinib.

Chest imaging obtained 2 months into alectinib therapy revealed further decrease in the size of the primary lung mass and thoracic lymphadenopathy as well as recurrence of the right pleural effusion and increased pericardial fluid (Fig. 2*C*). At this point, the patient was admitted to the hospital for worsening dyspnea. A right-sided tunneled pleural catheter was placed, yielding milky fluid (Figs. 1 and 3). Pleural fluid triglyceride level was 341 mg/dL, compatible with a chylothorax (Fig. 3*B* and Supplementary Table 2). Pericardial drainage was also pursued (Figs. 1 and 3) and yielded grossly serous pericardial fluid. Pericardial fluid triglyceride levels were not measured. Further pericardial interventions were not required during the course of the follow-up.

Alectinib was held and then restarted at 150 mg twice daily. Nevertheless, a tiered titration of the dose up

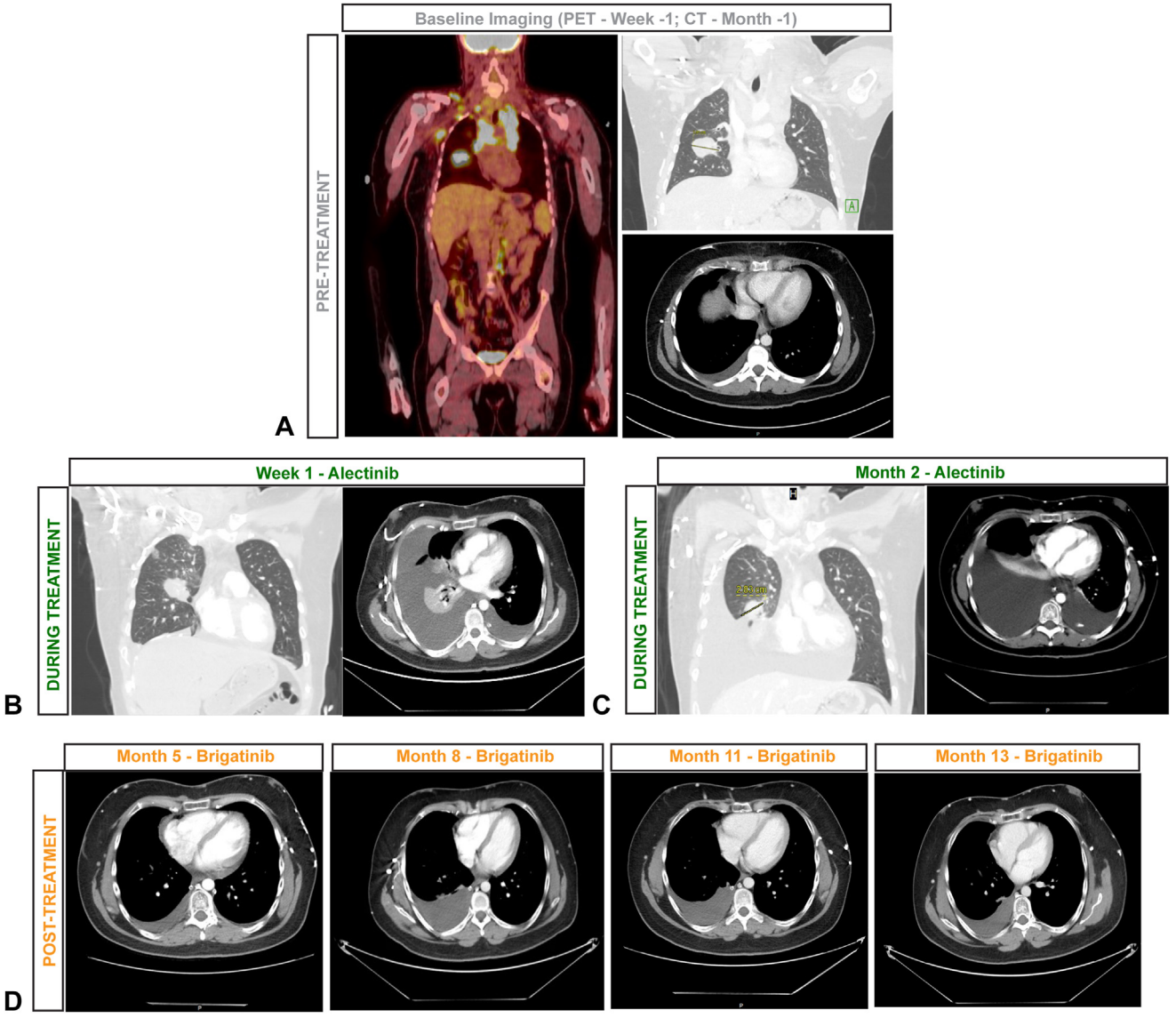

Figure 2. Pertinent chest imaging findings over the time course. (*A*) Baseline PET-CT and CT imaging obtained 1 week and 1 month prior to initiation alectinib therapy, respectively. PET-CT reveals intense FDG avidity in the primary tumor in the right lung and mediastinal and axillary lymphadenopathy; CT redemonstrates the primary tumor and a trace right-sided pleural effusion. (*B*) CT imaging obtained 1 week into alectinib therapy reveals significant increase of the right-sided and emergence of a left-sided pleural effusions. (*C*) CT imaging 2 months into alectinib therapy demonstrates persistent, large, bilateral pleural effusions. (*D*) Serial CT imaging obtained 5, 8, 11, and 13 months after alectinib initiation and during brigatinib therapy, demonstrating diminished bilateral pleural effusions. CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

to 450 mg twice daily was associated with an increase in pleural fluid output and pleural fluid triglyceride level (Fig. 3 and Supplementary Table 2).

Three months into therapy, alectinib was discontinued and brigatinib was initiated at the recommended dose of 90 mg daily followed by 180 mg daily. During brigatinib therapy, both fluid volume and triglyceride levels from the bilateral tunneled pleural catheters gradually decreased (Fig. 3 and Supplementary Table 2). Ultimately, spontaneous pleurodesis was achieved, allowing removal of the left-sided catheter and the right-sided catheter 6 and 11 months after placement, respectively (Figs. 2*D* and 3). Follow-up imaging 4 months after removal of the right catheter showed stable trace bilateral pleural effusions without evidence of reaccumulation and no evidence of progressive neoplastic disease (Supplementary Table 3).

Discussion

Spontaneous, nontraumatic, chylous effusions are extremely rare. There is, however, increasing evidence linking therapy with certain TKIs and the development of these effusions.

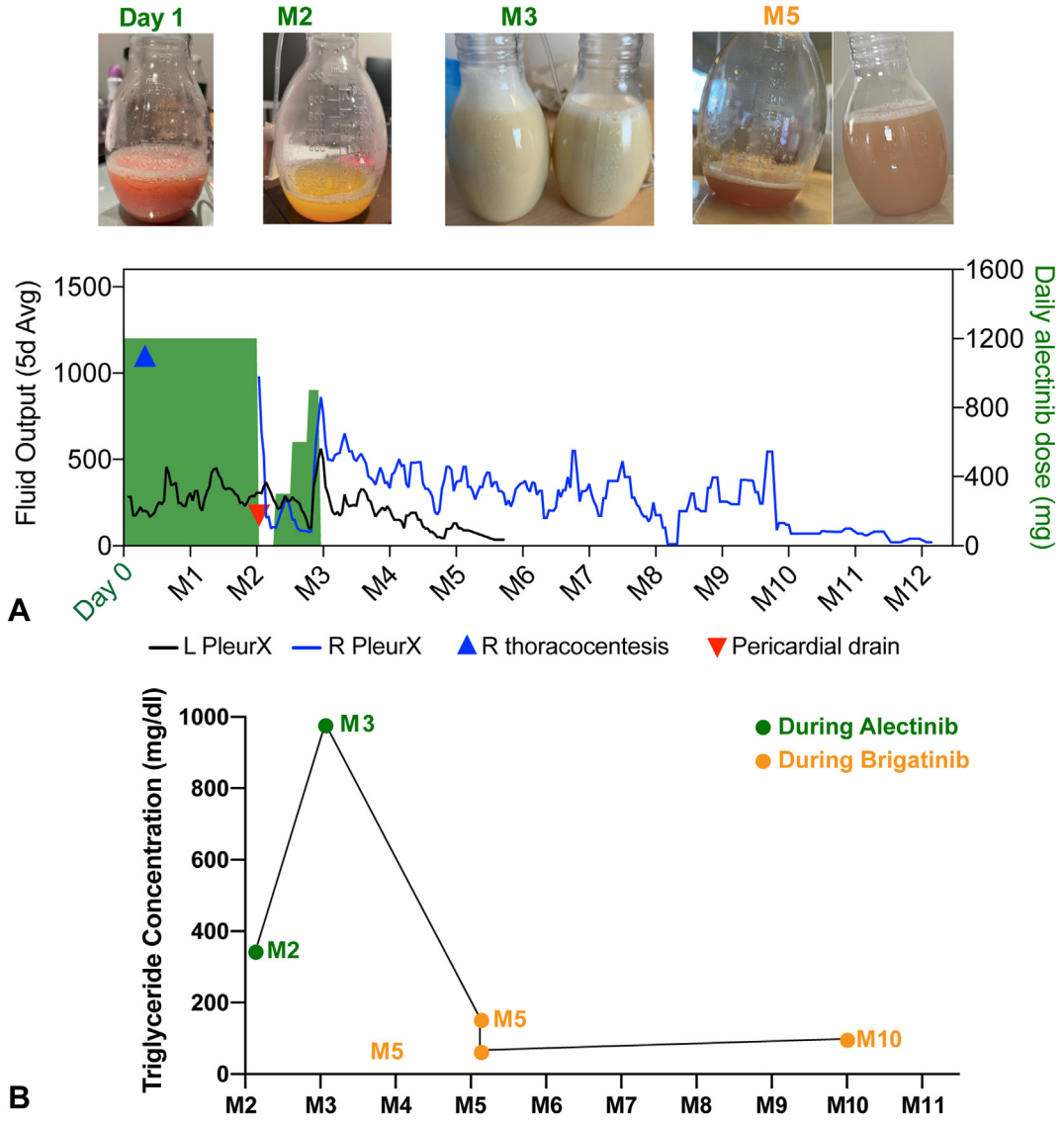

Figure 3. Quantification of pleural effusion volume and triglyceride level. (*A*) Illustrative images of pleural fluid gross appearance along the course of therapy. Green and orange color coding indicates fluid obtained during alectinib and brigatinib therapy, respectively. The line plot depicts a quantification of 5-day averages of pleural fluid volume drained from the left (black line) and right (blue line) indwelling pleural catheters. The volume of fluid drained from a right thoracocentesis (blue arrow) and pericardial drain (red arrow) are also indicated. Green shading indicates the cumulative daily alectinib dose in mg (right ordinate). The time scale starts at the index date and the subsequent months. (*B*) Line plot illustrating the pleural fluid triglyceride levels in mg/dL obtained 2, 3, 5, and 10 months after alectinib therapy initiation. Green and orange color coding indicates pleural fluid samples obtained during alectinib and brigatinib therapy, respectively. The time scale indicates months after alectinib therapy initiation. 5d Avg, 5-day average; M, month.

The multi-TKI, dasatinib, which inhibits kinases indicated in lymphoid tissue development, such as Src family kinases, PDGFRβ,[5,6] and BCR-ABL, has been noted to be associated with spontaneous chylothoraxes in multiple studies.[7] Our group has previously described the occurrence of nonmalignant chylothorax and chylous ascites in patients with various neoplasms, during the course of treatment with the selective and nonselective RET TKIs, selpercatinib, agerafenib, cabozantinib, and lenvatinib.[3] Although overall rare, the frequency of chylous effusions ranged from 0.2% with lenvatinib to 7% with selpercatinib, indicating that RET inhibition may be linked to spontaneous emergence of chylous effusions. The observation that chylous effusions are most frequently observed in patients treated with the selective RET TKI selpercatinib was later mirrored by other studies.[8] More recently, cases of chylous effusion were described during therapy with another selective RET TKI, pralsetinib.[9]

The underlying mechanism resulting in third spacing of chylous fluid during TKI therapy remains to be elucidated. The proto-oncogene *RET* has been found to be involved in development of intestinal lymphoid tissue as evidenced by the loss of lymphoid tissue in $RET^{-/-}$ mice.[10] Off-target RET signaling inhibition by alectinib[4] may therefore be one plausible mechanism of lymphatic drainage derangement. This hypothesis is further supported by the resolution of chylous fluid accumulation after alectinib discontinuation and during therapy with brigatinib, which does not harbor anti-RET activity.[11] Further studies are needed to explore the clinical extent of this adverse event and the underlying pathophysiology.

The emergence of pleural effusions, particularly spontaneous chylous effusions, in a patient with metastatic malignancy is often attributed to disease progression and may result in changes in cancer-directed therapy. An important cause of chylothorax that must be considered in the setting of thoracic metastatic disease is possible obstruction of the thoracic duct and subsequent obstructive chylothorax. These are generally unilateral and are particularly associated with hilar lymphadenopathy.[12] In contrast, the bilateral chylous effusions that persisted long after resolution of lymphadenopathy in our case highlight the importance of considering other, more infrequent, etiologies such as drug-induced chylothorax. Dose reduction or drug discontinuation are possible management strategies for drug-induced chylothorax.[9,13] Nevertheless, consistent with our previous report,[3] dose reduction was not effective in attenuating chylous fluid accumulation in this patient. When transition to an alternative agent is not feasible or desired, other management alternatives for chylothorax can be considered. These include lifestyle modifications, such as fat-modified diets, tunneled pleural catheter placement, chemical or surgical pleurodesis procedures, and certain medications, such as octreotide or midodrine.[14,15]

Conclusions

This case represents the first report of spontaneous, bilateral, nonmalignant chylothoraces that emerged during therapy with the ALK/RET inhibitor alectinib. The chylous effusions resolved after alectinib discontinuation and transition to brigatinib, an ALK TKI without anti-RET activity. It is important to recognize chylous effusions as a potential rare adverse event that may emerge during therapy with certain TKIs and avoid misattribution of this complication to neoplastic disease progression. Larger studies addressing the possible underlying mechanisms of TKI-related chylous effusion occurrence are required to extensively characterize this phenomenon and design more comprehensive management strategies.

CRediT Authorship Contribution Statement

Sunanjay Bajaj: Conceptualization, Visualization, Writing—Original draft preparation, Writing—Reviewing and editing.

Andrew Chow: Conceptualization, Writing—Reviewing and editing.

Alexander Drilon: Conceptualization; Writing—Reviewing and editing; Supervision.

Or Kalchiem-Dekel: Conceptualization; Writing—Reviewing and editing; Supervision.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at 10.1016/j.jtocrr.2023.100606.

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