Hyperprogression after Acquisition of Resistance Mutation to Alectinib in a Patient with Lung Adenocarcinoma: Case Report

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Hiperprogressão após Aquisição de Mutação de Resistência ao Alectinibe em Paciente com Adenocarcinoma de Pulmão: Relato de Caso

Hiperprogresión tras la Adquisición de una Mutación de Resistencia a Alectinib en un Paciente con Adenocarcinoma de Pulmón: Informe de Caso

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ABSTRACT

Introduction: The mutation in the gene anaplastic lymphoma kinase (ALK) occurs in approximately 3% to 5% of patients with lung adenocarcinoma, being more frequent in younger patients, non-smokers, or light smokers. Due to its molecular specificity, treatment involves the use of targeted therapies with ALK inhibitors, such as alectinib and lorlatinib, which have shown significant efficacy in blocking the abnormal activity of the protein. **Case report:** Young male patient diagnosed with metastatic lung adenocarcinoma to the pleura, associated with a genetic rearrangement of the ALK gene, featuring a new early mutation. The study describes the treatment with targeted therapies and clinical complications throughout the course of the disease. Due to complications and limitations for invasive interventions, the patient died one year and two months after his diagnosis. **Conclusion:** The study reinforces the importance of early diagnosis with specific tests and highlights the challenges of treatment, discussing new therapies and their obstacles to improve survival rates in advanced tumors.

Key words: Adenocarcinoma of Lung; Oncogene Fusion; Oncogene Proteins; High-Throughput Nucleotide Sequencing.

RESUMO

Introdução: A mutação no gene quinase de linfoma anaplásico (ALK) ocorre em cerca de 3% a 5% dos pacientes com adenocarcinoma de pulmão, sendo mais frequente em pacientes mais jovens, não fumantes ou fumantes leves. Em razão da sua especificidade molecular, o tratamento envolve o uso de terapias-alvo com inibidores de ALK, como alectinibe e lorlatinibe, que demonstram eficácia significativa ao bloquear a atividade anormal da proteína. **Relato do caso**: Paciente jovem, do sexo masculino, diagnosticado com adenocarcinoma pulmonar metastático para pleura, associado ao rearranjo genético do gene ALK, com nova mutação precoce. O estudo descreve o tratamento com terapias-alvo e as intercorrências clínicas observadas ao longo do curso da doença. Por causa de complicações e limitações por intervenções invasivas, o paciente evoluiu para o óbito após um ano e dois meses de seu diagnóstico. **Conclusão:** O estudo reforça a importância do diagnóstico precoce com exames específicos e os desafios do tratamento, debatendo sobre terapias novas e seus desafios, a fim de aumentar a taxa de sobrevida em neoplasias avançadas.

Palavras-chave: Adenocarcinoma de Pulmão; Fusão Oncogênica; Proteínas Oncogênicas; Sequenciamento de Nucleotídeos em Larga Escala.

RESUMEN

Introducción: La mutación en el gen quinasa de linfoma anaplásico (ALK) ocurre, en aproximadamente, del 3% al 5% de los pacientes con adenocarcinoma de pulmón, siendo más frecuente en pacientes jóvenes, no fumadores o fumadores ocasionales. Debido a su especificidad molecular, el tratamiento implica el uso de terapias dirigidas con inhibidores de ALK, como alectinib y lorlatinib, que han demostrado una eficacia significativa al bloquear la actividad anormal de la proteína. **Informe del caso:** Paciente joven, de sexo masculino, diagnosticado con adenocarcinoma pulmonar metastásico en la pleura, asociado con la reorganización genética del gen ALK, con una nueva mutación precoz. El estudio describe el tratamiento con terapias dirigidas y las complicaciones clínicas observadas a lo largo del curso de la enfermedad. Debido a complicaciones y limitaciones por intervenciones invasivas, el paciente evolucionó hacia el óbito un año y dos meses después de su diagnóstico. **Conclusión:** El estudio refuerza la importancia del diagnóstico temprano mediante exámenes específicos y destaca los desafíos del tratamiento, debatiendo sobre nuevas terapias y sus dificultades con el objetivo de aumentar la tasa de supervivencia en neoplasias avanzadas.

Palabras clave: Adenocarcinoma del Pulmón; Fusión de Oncogenes; Proteínas Oncogénicas; Secuenciación de Nucleótidos de Alto Rendimiento.

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INTRODUCTION

According to the Brazilian National Cancer Institute (INCA)[1], for each year of the 2023-2025 triennium, lung cancer is the third most common type among men in Brazil, with 18,020 new cases, and the fourth among women, with 14,540 new cases. On a global scale, it ranks first among men and third among women.

Adenocarcinoma, part of the group of non-small cell lung cancer (NSCLC), is the most common histological subtype, representing over 50% of all lung cancer types[2]. Unlike the small-cell type, adenocarcinoma is prevailing in non-smokers[3]. Clinical manifestations include persistent cough, dyspnea, fatigue, hemoptysis, and susceptibility to infections[4].

The anaplastic lymphoma kinase (ALK) gene on chromosome two encodes the tyrosine-kinase transmembrane that expresses the ALK protein. Its mutations and translocations produce an oncogenic ALK protein that activates signaling routes responsible for cell control[3]. The treatment is based on targeted therapy with anti-ALK tyrosine-kinase inhibitors and eventually chemotherapy. Other options include a combination with radiotherapy[5].

Given this context, this report aims to approach the importance of specific tests and challenges of targeted therapy treatment, contributing to managing advanced neoplasms. This case report was elaborated from the clinical observation of a patient hospitalized in the oncology ward of the *Fundação Hospitalar de Blumenau/ Hospital Santo Antônio* in 2024, who ended up dying.

This descriptive, observational, qualitative study follows the ethical guidelines for case reports, with informed consent obtained from the patient's legal guardian. After approval from the Research Ethics Committee (CEP), the patient's family member was contacted by phone for application of the Informed Consent Form (ICF) and provision of a Guardian Awareness and Consent Statement. The medical record in the Tasy system of the *Fundação Hospitalar de Blumenau* was then analyzed, and relevant information was collected.

The data was compiled, and a bibliographical review of articles found in SciELO, PubMed, Scopus, Google Scholar, and LILACS databases was conducted. The inclusion criteria concerned the studied population, intervention applied regarding the clinical case, full text availability, journal indexation, and recent publication date. Exclusion criteria were outdated studies and inadequacy of the analyzed population.

This article has been approved by the Research Ethics Committee, report number 7244620 (CAAE (submission for ethical review): 83720224.0.0000.5359), in compliance with Resolution 466/2012[6] of the National Health Council.

CASE REPORT

Male patient, L. M., Caucasian, 42 years old, Eastern Cooperative Oncology Group scale (ECOG 1), no previous comorbidities, and a negative previous history of smoking, seeks medical care in the public service due to dyspnea and progressive cough in June 2023.

A computed tomography angiography of the chest from July 24, 2023, presented a nodule measuring 25 x 28 mm in the right middle lobe, multiple sparse nodules, mediastinal lymph node enlargement, moderate pleural effusion on the right and pulmonary thromboembolism in the left lower lobe (treatment with rivaroxaban was initiated for thromboembolism). The carcinoembryonic antigen (CEA) was high at 6.67 ng/mL (reference value < 5.0), and the pleural biopsy confirmed pulmonary adenocarcinoma with clinical staging IV.

The patient, through the gratuity platform and access to genetic tests, performed the FoundationOne Cdx test, which identified a pathogenic mutation in the ALK – EML 4-ALK fusion (variant 3a/b), in addition to one-off mutations in CTNNB1, loss of MTAP, loss in CDKN2A/B, and one-off mutation in TP53 R306* with a frequency of variant allele of 15.1%. The test suggested a possible response to medications: alectinib, brigatinib, ceritinib, crizotinib, lorlatinib, and entrectinib.

First-line therapy started on September 1st, 2023, with alectinib 600 mg twice a day, initially acquiring the medication with own resources and later through a lawsuit, considering that such medication is not supported by the Brazilian healthcare service, presenting no side effects. There was a reduction of 29% CEA, falling back to the normality range with a result of 4.73 on December 6, 2023. A new tomography on January 5, 2024 showed a great partial response, with a small pleural effusion to the right and a reduction of 89% in the greatest diameter of pulmonary nodules, now measuring a maximum of 3 mm (Figure 1).

In February-March 2024, due to an interruption of the medication supply, the patient spent 30 days untreated and developed considerable dyspnea, needing hospitalization and oxygen therapy. There was a 250% increase in CEA to 16.6 on March 27, 2024 and a new chest tomography from April 21, 2024 showed a relevant increase in the tumoral volume, with obscuration of the entire right hemithorax by a

heterogeneous mass, with contrast enhancement and hypodense/liquefied areas in between, in addition to the appearance of axillary lymph node enlargement on the right (Figure 2).

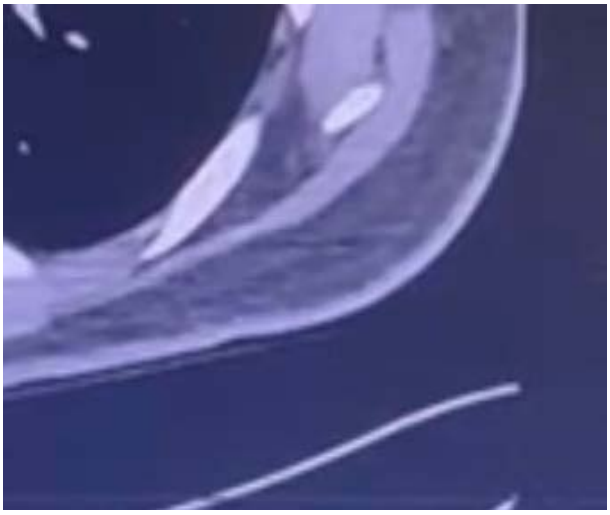

Figure 1. Chest tomography with contrast (1/5/2024) showing a small pleural effusion to the right and reduction of 89% in the diameter of the bigger pulmonary nodules, measuring a maximum of 3 mm

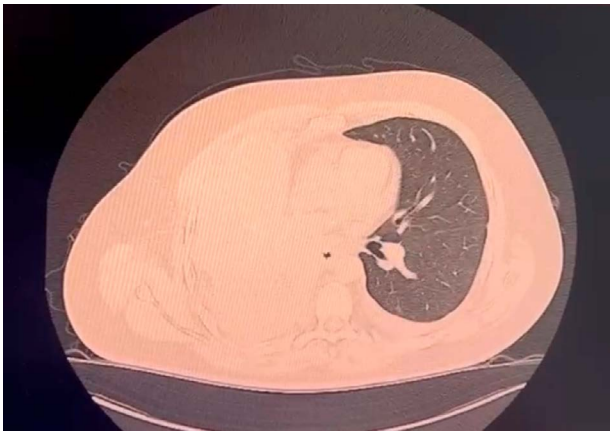

Figure 2. Chest tomography with contrast (4/21/24) showed a relevant increase in the tumoral volume, with obscuration of the entire right hemithorax by a heterogeneous mass, with contrast enhancement and hypodense/liquefied areas in between, in addition to the appearance of axillary lymph node enlargement on the right.

The adenomegalies were biopsied to exclude the hypothesis of lymphoproliferative disease, given the rapid tumoral growth, confirming the adenocarcinoma. After discussing the case in a multidisciplinary meeting, the team deliberated the start of a chemotherapy cycle with a triplet scheme (carboplatin + docetaxel + pemetrexed), considering hyperprogression and visceral crisis. The tissue was sent to a new broad genetic panel. A partial clinical improvement was observed, enabling hospital discharge.

In May, the patient was hospitalized again for a second chemotherapy cycle, however, he presented a generalized edema and worsened dyspnea, possibly due to the previous chemotherapy scheme's toxicity. On May 28, 2024, the patient developed a relevant ventilatory failure, associated with a multiresistant infection of *Pseudomonas aeruginosa* detected from a tracheal aspiration, needing orotracheal intubation and transfer to the intensive care unit (ICU).

The result of the new somatic test showed acquisition of resistance mutation in the ALK gene, now with a one-off mutation on G1202R, in addition to six new mutations in a very short time (CCND1, EMSY, FGF19, FGF3, FGF4, KMT2A), conferring possibilities of resistance to alectinib and sensibility to lorlatinib only. The patient acquired lorlatinib, and a new treatment was started in the ICU on June 2, 2024, through a nasogastric probe, following similar work and paying attention to medication interaction with fluconazole.

During his stay in the ICU, the patient needed chest drainage (due to pneumothorax after central venous access), tracheostomy, broad-spectrum antibiotics, and fungicidal treatment due to candidemia. The patient showed the first signs of disease volume decrease after eight days of treatment, in a chest tomography of June 11, 2024, that reported a reduction of pleural effusion to the left and a discrete reduction of consolidated area of the right lung, in addition to mechanical ventilation weaning, after 28 days, allowing ICU discharge on July 4, 2024.

After two days in the nursery ward, there was a new ventilatory worsening, with a PCR analysis collected through tracheal aspiration showing the multiresistant infection by *Pseudomonas aeruginosa* persisted, now presenting the ultraresistant mechanism, which would require the use of significantly more costly antibiotics, which were not used, in addition to the presence of parainfluenza virus, associated with the tracheal aspiration culture with *Serratia* ESBL (extended-spectrum beta-lactamases) and urine culture with *Escherichia coli* ESBL. Therapy with antibiotics was restored, coupled with mechanical ventilation, and the 60-day treatment with lorlatinib was completed.

The patient also presented a possible depressive case, a side effect described in 22.7% of patients using lorlatinib (according to the package insert[7]). After a multidisciplinary discussion, the team suspended the oncological treatment to focus on comfort measures. The patient died on August 4, 2024, 11 months after starting treatment and after being hospitalized for approximately three months.

DISCUSSION

First, it is important to highlight that the patient came from the public healthcare system, which, despite not excluding the possibility of access to targeted therapy, presents challenges in managing complex cases, as the one reported, resulting in potential delays in treatment and favoring disease progression. Thus, diagnosis is the fundamental basis of oncological treatment. At first, tumors were only diagnosed through immunohistochemical tests for ALK, which provided limited information, just as the FISH applied to one gene, omitting important data for patient treatment.

As mentioned earlier, the FoundationOne CDx test is a new generation sequencing (NGS) test that precisely detects the main types of genomic alterations, in addition to complex biomarkers, like microsatellite instability, mutational load, and tumoral fraction[8]. For this patient, his variant 3a/b indicated from the start an unfavorable clinical response [9], although ALK tumors tend to have a better prognosis with the new lines of treatment[10].

Similarly, TP53 mutation favors the loss of the DNA verification mechanism, favoring the development of new mutations[11], as seen in this patient. Regarding epidemiology, 44.5% of patients with adenocarcinoma are male, with an average five-year survival rate of 20%, and its progression is marked by cellular heterogeneity[4]. Regarding treatment, tyrosine-kinase inhibitors (TKI) are considered a first-line treatment, and over 15 drugs are currently approved by the Food and Drug Administration (FDA) for seven oncogenic drivers in NSCLC[12].

The CROWN study made a five-year follow-up comparing the lorlatinib and crizotinib drugs, showing the superior effectiveness of lorlatinib for patients with advanced NSCLC and ALK-positive. The results showed significant benefits in progression-free survival, characterizing the longest follow-up ever reported in molecular therapy for metastatic solid tumors[10].

In contrast, one risk of ALK inhibitors is resistance to the medication due to cancer cells accumulating new mutations, which makes the treatment extremely complex. The explanations for this early resistance, mentioned in some works as up to three months, may be attributed to the high load of tumoral mutation and tumor heterogeneous evolution, a potent strategy being the combined therapy with ALK inhibitors[13]. It is important to highlight that interrupting the initial treatment for 30 days can also be considered a relevant factor for mutation and early resistance.

CONCLUSION

Although the outcome was unfavorable, the use of alectinib enabled good symptom control until the first pause in the treatment. Later, supported by complementary strategies, it was possible to reach mechanical ventilation weaning while using lorlatinib. However, there were unfavorable influences in the clinical condition, like an uncontrolled infection and medication administration through a nasogastric probe, which also contributed to the unfavorable outcome.

Given this, NGS has provided increasingly relevant information for prognosis stratification of advanced neoplasms, in addition to enabling the prediction of response rates and disease control time.

Thus, in the context of lung adenocarcinoma, requesting NGS has become increasingly indispensable in every metastatic case, with a broad and detailed reading of results. We also highlight the importance of performing a periodical reassessment of the mutational profile of patients in targeted therapy treatments.

CONTRIBUTIONS

Both authors have substantially contributed to the study design, acquisition, analysis, and interpretation of the data, wording, and critical review. They approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

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