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Osimertinib: A Game-Changer in Stage IV EGFR-Driven Lung Cancer

Osimertinib: Um Ponto de Viragem no Cancro do Pulmão EGFR Positivo em Estádio IV

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ABSTRACT

Lung cancer has a high mortality rate; however, treatment with tyrosine kinase inhibitors targeting specific molecular alterations has significantly improved the survival of patients with advanced or metastatic non-small cell lung carcinoma (NSCLC). EGFR mutations are present in approximately 15% of NSCLC cases. Osimertinib was approved in Portugal by Infarmed (Portuguese Medicines Agency) in 2021 as a first-line therapy for advanced NSCLC with EGFR sensitizing mutations. A 55-year-old man, a former smoker, presented to the Emergency Department with a six-month history of dry cough and dyspnea that had worsened and was now accompanied by fever. Chest CT revealed multifocal pulmonary consolidations that were already present in a scan performed three months earlier. Bronchial biopsies confirmed a diagnosis of lung adenocarcinoma with an EGFR exon 19 deletion. Staging tests revealed stage IV-A disease (pulmonary metastasis and, later, right adrenal metastasis identified on PET-FDG). The patient was started on osimertinib. He was discharged and progressively recovered his baseline general condition, achieving a performance status of 0 and resuming physical activity. Despite the extensive thoracic disease, the patient achieved a complete metabolic response documented on PET-CT five months after initiating therapy, along with significant clinical improvement. Osimertinib effectively inhibits the EGFR signaling pathway and has been established as the first-line treatment for patients with stage IV disease since the FLAURA trial. However, such complete responses are rare and raise further questions about the factors influencing these responses, the optimal duration of therapy in these cases, and the role of circulating tumor DNA in therapy monitoring and discontinuation decisions.
Keywords: Carcinoma, Non-Small-Cell Lung/drug therapy; ErbB Receptors; Lung Neoplasms/drug therapy; Osimertinib

RESUMO

Apesar de o cancro do pulmão apresentar uma elevada taxa de mortalidade, o tratamento com inibidores de tirosina-cinase dirigidos a determinadas alterações moleculares, tem melhorado a sobrevivência dos doentes com carcinomas de não-pequenas células (CPNPC) avançado ou metastático. As mutações do EGFR estão presentes em cerca de 15% dos CPNPC. Em Portugal, o osimertinib foi aprovado pelo Infarmed em 2021 como primeira linha terapêutica no CPNPC avançado com mutações sensibilizadoras do EGFR. Um homem de 55 anos, ex-fumador, com sintomas tosse seca e dispneia com seis meses de evolução, recorreu ao Serviço de Urgência por agravamento das queixas e febre. A tomografia computorizada torácica revelou consolidações pulmonares multifocais, já presentes no exame realizado três meses antes. Foram realizadas biópsias brônquicas compatíveis com adenocarcinoma do pulmão com deleção do exão 19 do EGFR. Os exames de estadiamento revelaram estádio IV-A (metastização pulmonar e, posteriormente em PET-FDG, suprarrenal direita) e foi iniciado osimertinib. O doente teve alta e progressivamente recuperou o seu estado geral prévio. Apesar de doença torácica extensa, o doente atingiu resposta metabólica completa, documentada em PET-TC após cinco meses do início da terapêutica, com melhoria clínica significativa. O osimertinib bloqueia eficazmente a via de sinalização do EGFR, sendo o tratamento de primeira linha nos doentes com CPNPC EGFR positivo avançado ou metastático desde o estudo FLAURA. Contudo, este tipo de resposta completa é raro e levanta-nos outras questões que realçam a necessidade de mais investigação sobre os fatores que influenciam este tipo de resposta, a duração da terapêutica nestes casos e o papel do DNA tumoral circulante na monitorização da terapêutica e decisão de suspensão.
Palavras-chave: Carcinoma Pulmonar de Células não Pequenas/tratamento farmacológico; Neoplasias do Pulmão/tratamento farmacológico; Osimertinib; Receptor ErbB-2

INTRODUCTION

Lung cancer is the third most prevalent cancer in Portugal, yet it remains the leading cause of death from oncological diseases.[1,2] Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of cases, with adenocarcinoma being the most prevalent subtype. Biomarkers increasingly guide treatment decisions, leading to improvement in response rates, survival outcomes, and quality of life. Epidermal growth factor receptor (EGFR) mutations are the most common oncogenic drivers in NSCLC, occurring in approximately 15% of lung adenocarcinomas in Europe.[2] Osimertinib has been approved in Portugal as a first-line treatment for locally advanced or metastatic EGFR-positive lung carcinomas since 2021, following the results of the FLAURA clinical trial.[3] In this trial, the efficacy of osimertinib was compared to gefitinib or erlotinib (first-generation tyrosine kinase inhibitors) as first-line therapy for EGFR+N SCLC. The majority of patients achieved a partial response (77%), with only seven patients exhibiting a complete response, as assessed by RECIST criteria.[4]

CASE-REPORT

A 55-year-old man with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 (symptomatic but fully ambulatory), history of dyslipidemia and a former light smoker (five pack-years), presented at the Emergency Department (ED). He had a six-month history of progressive

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dry cough and exertional dyspnea, classified as grade 2 (walks slower than people of the same age because of dyspnea) on the modified Medical Research Council (mMRC) scale, with considerable worsening over the prior week, accompanied by fever and, in the previous three days, yellowish sputum. A chest computed tomography (CT) performed approximately three months after symptom onset revealed an extensive multilobe consolidation with air-bronchogram in the left lung. The patient's condition remained unresolved after two antibiotic courses, and he awaited further evaluation. He presented at the ED with a Glasgow Coma Scale of 15, a respiratory rate of 28 cycles per minute, and was unable to complete sentences. Cardiac auscultation revealed rhythmic heart sounds without murmurs, while lung auscultation showed diminished vesicular murmur in the left lower third, with crackles. Arterial blood gas analysis on room air (FiO_2 21%) demonstrated severe type 1 respiratory failure, with a paO_2 of 49 mmHg (RV > 70 mmHg). Blood tests revealed mild leukocytosis (10 230 cells/µL) and a CRP of 5.8 mg/dL. Progressive increases in oxygen supplementation were required during the first hours of admission, with a paO_2 of 67 mmHg on FiO_2 60%, which led to admission to the intensive care unit. A bacterial superinfection was assumed, and the patient started empirical antibiotic therapy with amoxicillin/clavulanate and azithromycin.

The patient tested positive for respiratory syncytial virus, and a new chest CT showed extensive multifocal consolidation and numerous bilateral ground-glass opacities (Fig. 1). Despite starting high-flow oxygen, the patient quickly deteriorated and was placed on invasive mechanical ventilation. After stabilization of the clinical status, a flexible bronchoscopy was performed for further investigation. Since the patient had been experiencing symptoms for six months and, for at least three months, had an extensive persistent pulmonary consolidation on CT scan, in addition to the collection of material for microbiological analysis, transbronchial lung biopsies in the left lower lobe and lingula were performed. These revealed papillary lung adenocarcinoma with PD-L1 expression of 0% and cultural studies were negative. An EGFR exon 19 deletion (19del) was detected by Idylla® (a fully automated PCR-based system that enables rapid detection of genetic mutations), providing a faster diagnosis later confirmed by next-generation sequencing (glu746_Ala750del).

Staging tests with contrast-enhanced brain and upper abdominal CT scans, did not show extrathoracic metastasis. The case was discussed in a multidisciplinary tumor board, and the staging was determined as cT4NxM1a (IV-A) due to lesions in the contralateral lung already shown in the previously performed CT scan. Staging fluorodeoxyglucose (FDG) positron emission tomography (PET-FDG) was postponed due to the current infectious context. The patient

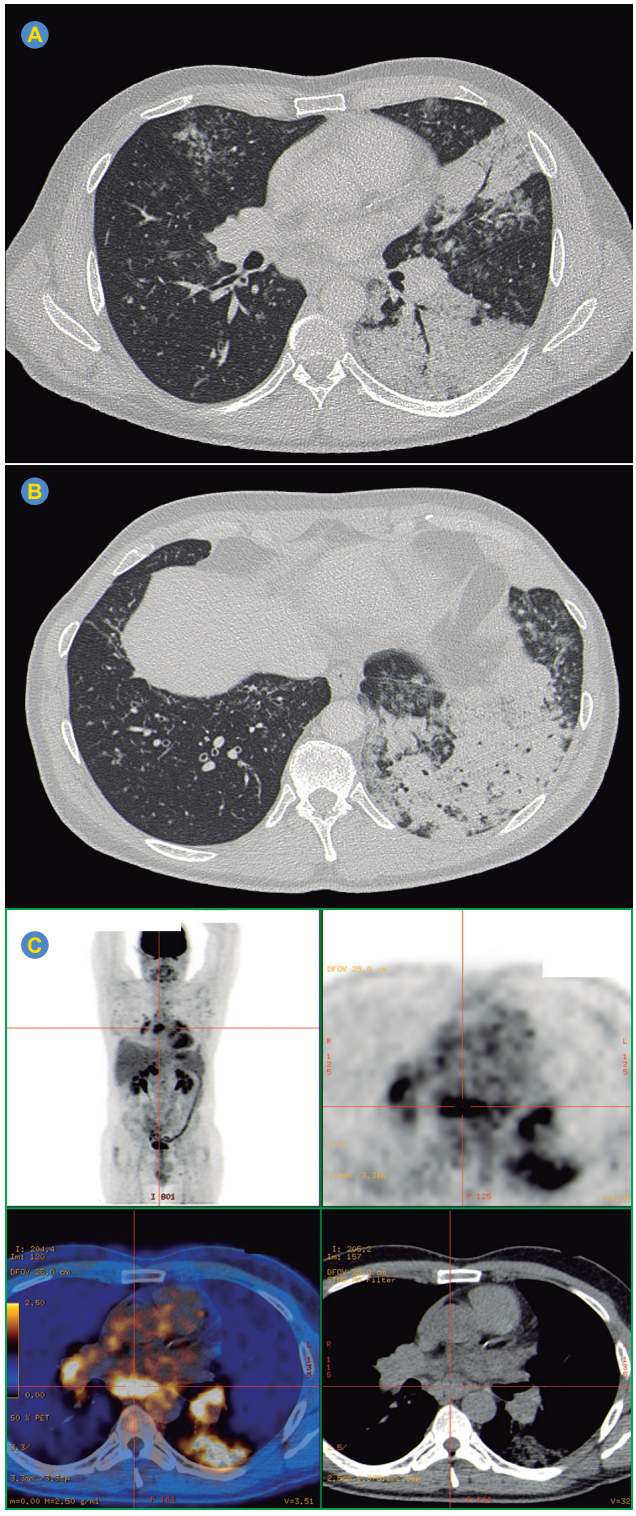

Figure 1 – Chest CT showing multifocal consolidation involving almost the entire left lower lobe and lingula, comprising approximately 50% of the left lung, as well as numerous bilateral ground-glass opacities (A) (B). PET-CT showing increased metabolic uptake in the left upper and lower lobes, right middle lobe, and bilateral lymph stations (10L, 7, 4L, 10R) (C).

was extubated after 48 hours. Given the extensive consolidation, thought to be neoplastic, and the respiratory failure, despite not completing staging, the patient started osimertinib 80 mg once daily and was discharged a few days later. Four weeks later, PET-FDG revealed increased metabolic uptake in the left upper and lower lobes (SUV 4.4 and 4.0, respectively), right middle lobe (SUV 1.8), bilateral lymph node stations (4L, 7, 10L, 10R with maximum SUV of 4.9) and in the right adrenal gland (SUV 8.0) (cT4N3M1b; IV-A; TNM 8th edition) (Fig. 1).

Five months after the onset of treatment, a chest CT revealed a significant improvement in the previously identified consolidation, with only a few bronchiolectasis and ground-glass opacities remaining in the left upper lobe and lingula. Additionally, a sparse fibrotic-cicatricial subpleural reticulation was observed. A subsequent FDG PET-CT confirmed a complete treatment response (Fig. 2).

The patient regained his previous overall health status, experienced gradual improvement in symptoms and eventually became asymptomatic. He resumed regular work and physical activities, exhibiting a PS 0 at the time of this report. The continued use of osimertinib has been well tolerated, with only grade 1 (mild and localized) cutaneous toxicity, assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), and treated with topical corticosteroids.

DISCUSSION

Osimertinib is a potent irreversible third-generation EGFR tyrosine kinase inhibitor. It binds covalently to the cysteine residue within the ATP-binding site of the EGFR kinase domain, preventing its autophosphorylation and downstream signaling pathways. By disrupting these crucial signaling cascades, osimertinib effectively stops EGFR's aberrant activation, leading to apoptosis of tumor cells.[4]

Currently, it is the standard first-line therapy for stage IV NSCLC patients carrying EGFR 19del.[5] In the FLAURA trial, although a high rate of patients exhibited stable disease or partial response, only 3% achieved complete response, highlighting the rarity of such outcomes.[4]

Takeyasu Y *et al* showed that patients with 19del had significantly higher response rates than patients with exon 21 *L858R* mutations. When comparing the distinct efficacy of first-line osimertinib according to mutation subtypes, patients with 19del had more often complete central nervous system (CNS) response (42% *vs* 25%) and a higher clinical benefit (97% *vs* 79%). Among 229 evaluated patients, only three exhibited complete systemic response (two with del19 and one with L858R).[6]

We present a rare case of a significant clinical response and complete treatment response to osimertinib as first-line therapy in a stage IVA NSCLC patient, despite initially documented extensive tumor lesions. The absence of CNS, pleural or hepatic metastases, along with the patient's favorable PS, may have contributed to the favorable prognosis. This case emphasizes the need for continued investigation on individual variations in treatment response, encouraging further research into factors contributing to complete remission. Treatment with osimertinib is recommended until disease progression or unacceptable toxicity. If the patient maintains this response pattern over time, it raises questions regarding the optimal duration of treatment and the absence of recommendations regarding the role of PET in these cases. Circulating tumor DNA (ctDNA) is already being used for EGFR mutation testing; however, it lacks sensitivity, particularly in cases with a low disease burden. As such, a tissue biopsy remains necessary if cfDNA results are negative. Nevertheless, its role in monitoring therapeutic response, predicting treatment outcomes, and enabling early detection of relapse or disease progression has gained increasing interest.[5,7] Could ctDNA play a role in monitoring response or in determining whether therapy could be suspended in these patients? There are clinical trials ongoing to determine the role of ctDNA in disease monitoring.[7] With the increasing accessibility of molecular testing and an increase in diagnosed EGFR-driven tumors, these sustained complete response patterns may become increasingly documented, which underscores the need for recommendations on how to manage these patients over time.

Ultimately, this case highlights the critical role of a precise diagnosis and comprehensive investigation, including mutational status, especially when facing high clinical suspicion scenarios and when patients present with critical illness, to promptly initiate therapy and improve patient outcomes.

AUTHOR CONTRIBUTIONS

SS: Literature review, writing of the manuscript.
JD: Writing of the manuscript.
CS, MF: Critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

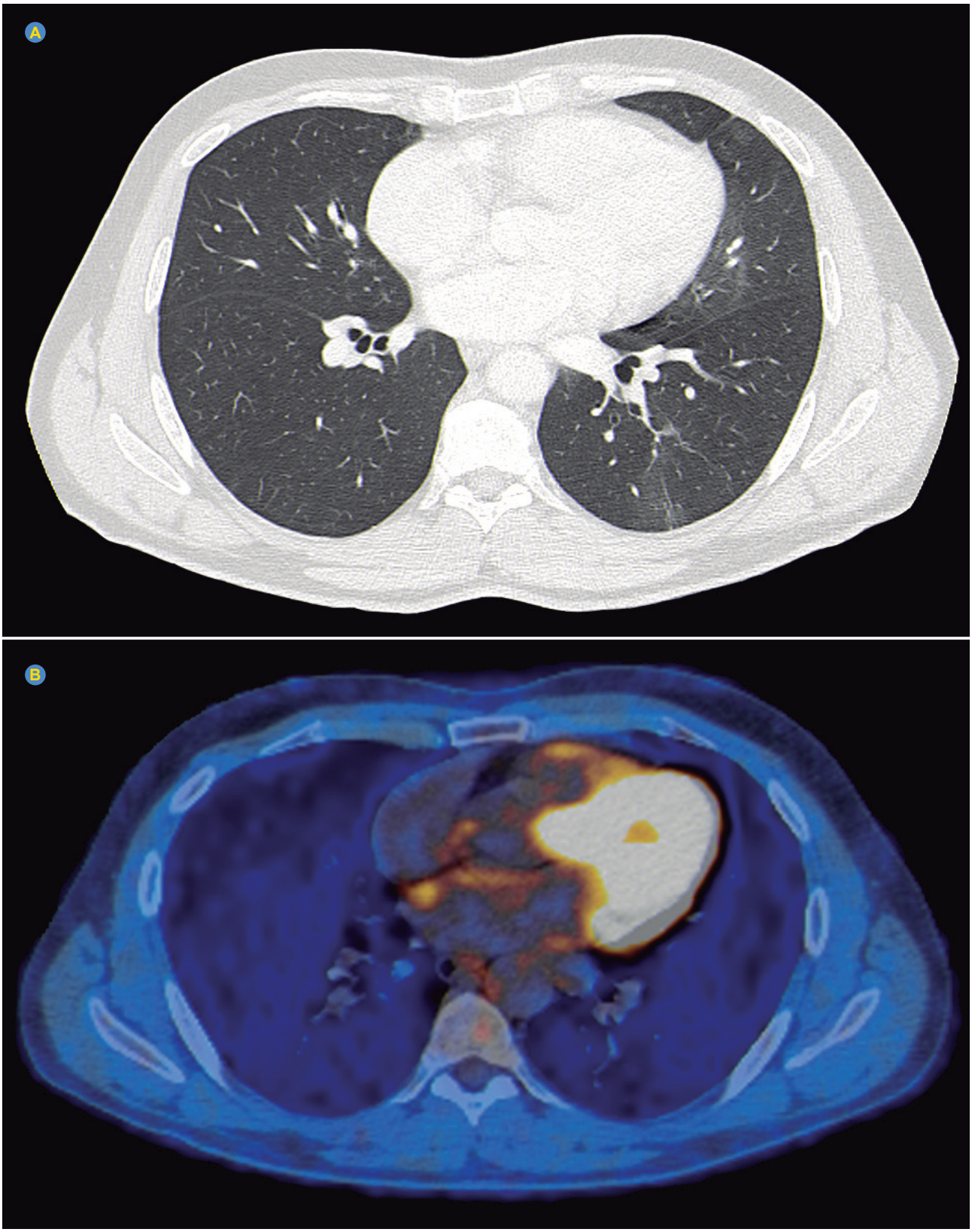

Figure 2 – Chest CT (A) and PET scan (B) showing complete metabolic response on the chest

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

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MF has declared that no competing interests exist.

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