



“Lazarus effect” in patient affected by lung adenocarcinoma carrying EGFR, CTNNB1, MET exon 11 and PIK3CA mutations treated with gefitinib

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Abstract: Lung cancer is the most commonly diagnosed tumor and the leading cause of cancer death. Molecular diagnosis allows the identification of different subgroups of non-small cell lung cancer (NSCLC), the so called “oncogene-addicted” cancers and determines therapeutic strategies for patients with non-small-cell lung cancer-adenocarcinoma (NSCLC-A). In fact, molecular profiling is now a well-established routine practice in patients with NSCLC. Next generation sequencing (NGS) allows to identify multiple concurrent mutations, whose clinical impact often remains unclear. EGFR tyrosine kinase inhibitors (EGFR-TKIs) have dramatically improved the outcomes of patients affected by EGFR-mutated lung adenocarcinoma. In our work, we report the case of a 60-years old female who was diagnosed with metastatic lung adenocarcinoma. NGS sequencing was performed and showed EGFR exon 19 deletion, CTNNB1 exon 3 mutation, MET exon 11 mutation and PIK3CA exon 2 mutation. We started first-line treatment with gefitinib (250 mg daily) achieving an immediate improvement in clinical condition (a so called “Lazarus effect”) and a partial response after only 7 days of treatment. The patient is still alive and on treatment with gefitinib after 7 months without signs of disease progression. Although concurrent mutations of CTNNB1, MET and PIK3CA are regarded as negative prognostic factors in patients affected by EGFR-mutated NSCLCs; our patient showed an impressive response to EGFR-TKI, suggesting that in our case EGFR acts as “driver mutation”. The presence of these specific concurrent mutations doesn't affect the response to EGFR-TKI.

Keywords: Case report; Lazarus effect; EGFR tyrosine kinase inhibitors; non-small cell lung cancer (NSCLC); precision medicine

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Introduction

Lung cancer is the most commonly diagnosed tumor across the globe (11.6%) and the leading cause of cancer death in both male and female (18.4%) (1).

Molecular characterization became a well-defined diagnostic procedure in patients carrying non-small cell lung cancer (NSCLC) and allows the diagnosis of specific

NSCLC sub-categories, the so called “oncogene-addicted” tumors. Patients carrying distinct gene mutations show significant differences in terms of clinical features and therapeutic opportunities (2). In fact, for some driving mutations, development of specific targeted therapies has now revolutionized the treatment of advanced disease.

In particular, EGFR tyrosine kinase inhibitors (EGFR-

TKIs) have dramatically improved the outcomes of patients affected by EGFR-mutated lung adenocarcinoma. On the other hand, NGS sequencing (Next Generation Sequencing) also allows the identification of multiple concurrent mutations, whose clinical impact often remains unclear. Currently there are not available treatments for CTNNB1 exon 3 mutations, PIK3CA exon 2 mutations and MET exon 11 mutations; on the other hand, osimertinib is the standard of care for EGFR-mutated metastatic lung adenocarcinoma. Recently, Food and Drug Administration (FDA) approved first line treatment with capmatinib for patients affected with NSCLC carrying MET exon 14 skipping mutations or MET amplifications (more than 10 gene copy number) (3).

We present the following article in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/pcm-20-32>).

Case presentation

Here we report the case of a 60-year-old lady, never smoker, admitted in pulmonology intensive care unit for acute respiratory distress and hypoxemia in December 2019. In November, she was previously misdiagnosed with pneumonia and treated with antibiotics (piperacillin-tazobactam 18 g daily for 10 days plus levofloxacin 750 mg daily for 10 days) and methylprednisolone (40 mg daily for 10 days) without improvement. EBUS-TBNA was performed and she was diagnosed with metastatic lung adenocarcinoma (stage IV).

During hospitalization, she experienced a worsening of respiratory function and needed high-flows oxygen (FIO₂ 80%) achieving only a partial correction of hypoxemia, with O₂ saturation of 87%. ECOG Performance Status was 3. She was also treated with amoxicillin/clavulanic acid (3 g daily for 1 week), azithromycin (500 mg daily for 10 days) and prednisolone (25 mg daily for 1 week) without clinical improvement.

During the recovery in pulmonology, comprehensive molecular profiling by NGS sequencing (OncoPrint Focus Assay, Kit RUO) was performed and showed EGFR exon 19 deletion, CTNNB1 exon 3 mutation, MET exon 11 mutation and PIK3CA exon 2 mutation.

Within few hours, after having obtained NGS results, we started first-line treatment with gefitinib (250 mg daily) achieving an immediate improvement in respiratory function and clinical condition (a so called “Lazarus effect”) while a CT scan performed 7 days after therapy’s start

showed a partial response (PR). The CT scan performed after 14 weeks of treatment (April 2020) confirmed the PR (Figures 1,2). The patient is still alive and on treatment with gefitinib. Moreover after 7 months from the diagnosis the patient shows no signs of disease progression.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

Discussion

The discovery of EGFR somatic mutations and the availability of potent and selective EGFR tyrosine kinase inhibitors (TKIs) have revolutionized NSCLC’s treatment (4) with impressive response such as the so called “Lazarus effect” (5).

Molecular profiling of NSCLC is currently an established routine practice in patients with advanced disease. Recently, NGS is progressively replacing sequential single gene assessment, leading to the discovery of a significant proportion of patients presenting multiple and concomitant molecular alterations, whose impact on prognosis and response to targeted agents remains often unclear.

Our clinical case showed 4 gene alterations, 3 of whom recognized as pathogenetic (EGFR, CTNNB1 and PIK3CA) and 1 (MET exon 11 mutation) of unclear biological significance.

While the predictive impact of EGFR is now well established, the significance of PIK3CA, MET exon 11 and CTNNB1 is still object of investigation.

Preclinical data of concurrent PIK3CA and EGFR mutations reported how the continuous activation of PI3K signalling by PIK3CA oncogenic mutant was sufficient to abrogate gefitinib-induced apoptosis in EGFR mutated NSCLCs cell line. Clinical studies showed no significant differences in objective response rate, median time to response, TTP, and duration of EGFR-TKI therapy in patients with EGFR and PIK3CA co-mutations. However, median overall survival (OS) was significantly shorter (18.0 vs. 33.3 months), suggesting that the PI3KCA pathway activation can be associated with EGFR-TKI resistance (6).

Regarding β -catenin, previous papers reported its main role in tumorigenesis, especially in the origin and

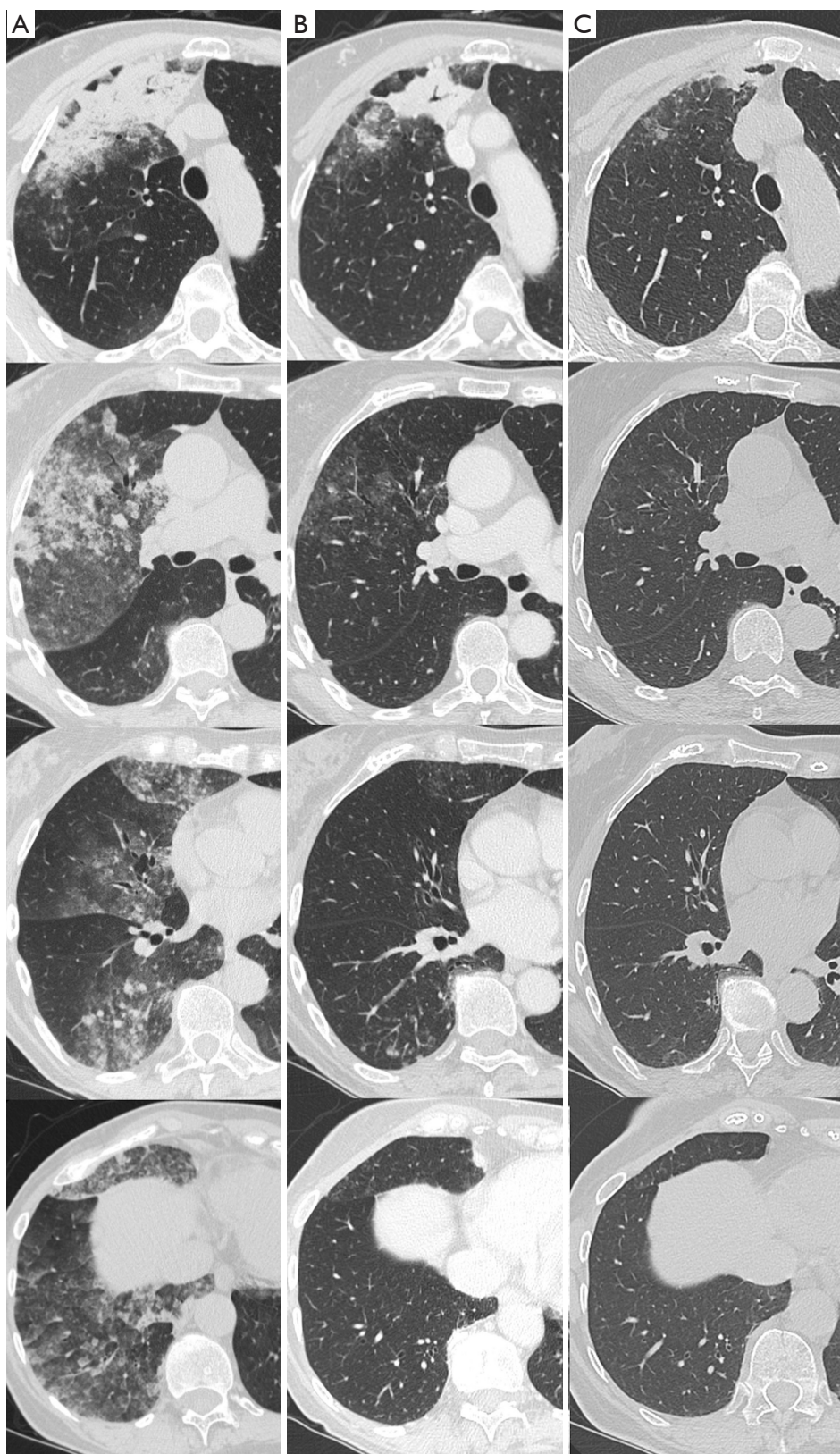


Figure 1 Response to treatment. (A) Basal CT scan; (B) CT scan after 1 week of treatment; (C) CT scan after 14 weeks of treatment.

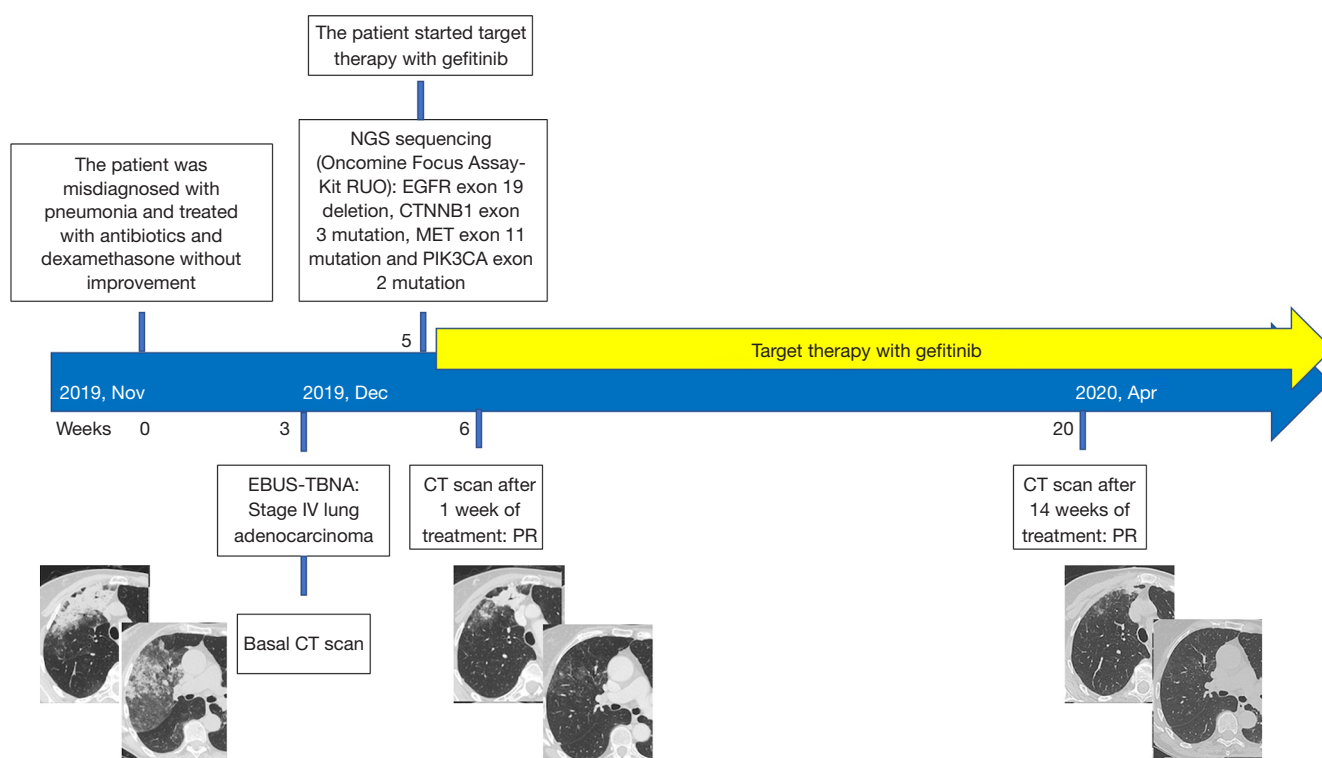


Figure 2 Timeline of patient's medical history.

development of lung cancers carrying EGFR resistance mutations. In fact, inhibition of β -catenin or deletion of CTNNB1 (β -catenin encoding gene) has been shown to reduce EGFR-L858R-T790M-mutated lung tumor growth both *in vitro* and *in vivo* (7).

Finally, while MET exon 14 skipping mutation is a recognized mechanism of resistance to EGFR-TKIs treatment in 5% to 26% of NSCLCs (8), MET exon 11 mutations are very uncommon and, therefore, their prognostic impact on EGFR-TKI activity in EGFR/MET co-mutated NSCLCs has not yet been assessed.

Conclusions

In clinical practice, the increasing use of NGS allows to identify a discrete proportion of NSCLC patients with multiple and concurrent molecular alterations, whose optimal treatment strategy remains unclear.

Although PIK3CA, CTNNB1 and MET co-mutations are all regarded as negative prognostic factors, being associated with EGFR-TKI resistance, a dramatic response to EGFR-TKI treatment was achieved in our clinical case, thereby suggesting that these co-mutations may act as

“passenger” molecular alterations and should not, therefore, affect clinical decisions.

In our opinion, among the strengths of our case report is the rarity of the clinical case. Indeed, our patient presents 4 concurrent mutations: 3 of which (MET, CTNNB1 and PIK3CA) have been shown to be associated with EGFR-TKI resistance in preclinical trials. The improvement of the precision oncology through NGS sequencing allows to identify multiple coexisting mutations, but some of them are adversely prognostic and not “targetable”. Further studies will be helpful to point out which of these mutations acts as prognostic or predictive factors, guiding the therapeutic strategy.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/pcm-20-32>

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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 studies involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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