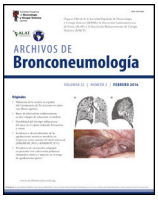
Arch Bronconeumol. 2019;55(5):268–281

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Scientific Letters

Accurate Identification of Predictive Biomarkers of Response to Targeted Therapies in Lung Cancer With Next Generation Sequencing

Identificación precisa de biomarcadores predictivos de respuesta a terapias dirigidas en cáncer de pulmón con secuenciación de nueva generación

Dear Editor,

Identification of molecular targets in non-small cell lung cancer (NSCLC) represents a major paradigm shift. Detection of *EGFR* mutations, present in 10–20%[1] of European NSCLC patients, predicts response to EGFR tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, afatinib or osimertinib. Although these drugs are highly effective in this selected population primary resistance can be observed in 30% of patients.[2] Molecular mechanisms implicated in primary resistance are currently being explored.[3] Additionally, resistance to these agents invariably develops after a median of 9.2–14.7 months,[4] process known as acquired resistance.

Here we describe the case of an 85-year-old male patient with an *EGFR* mutant lung adenocarcinoma who probably did not receive the best therapeutic approach. The patient was a never smoker. He had a history of hypertension, vitamin B12 deficiency associated anemia and osteoarthritis.

He presented in the emergency department with a 15-day history of dyspnea. On physical examination, he presented tachypnea and, on auscultation lung sounds were normal. Blood test showed no signs of infection. The computed tomography of the chest revealed a bilateral pulmonary embolism, as well as a solid mass measuring more than 7 cm in the right upper lobe, with enlarged lymph nodes at both mediastinal and ipsilateral hilar regions. Imaging also showed pleural effusion and bone, adrenal and liver lesions consistent with metastases. A liver biopsy was performed for diagnostic purposes.

While waiting for pathologic and molecular diagnosis the patient had progressive dyspnea and worsened hypoxemia, with a decline in the oxygen saturation. Non-invasive ventilation was initiated. As the patient was a non-smoker, a liquid biopsy was obtained for *EGFR* testing. Real-time PCR (Therascreen) results in 24 h detected an *EGFR* L858R mutation on exon 21. Treatment with gefitinib at 250 mg daily was initiated. Unfortunately, the patient failed to respond, and died after 7 days on treatment.

The pathological evaluation of the liver biopsy was consistent with a metastasis from a lung adenocarcinoma with PDL1 (28.8) positivity in 40% of cancer cells. The next generation sequencing (NGS) targeted panel Oncomine Focus Assay DNA and RNA showed the *EGFR* mutation on exon 21 (Fig. 1A) as well as a *MET* amplification with a *MET* copy number of 5.67 and a *TP53* mutation. This *MET* amplification was subsequently confirmed by FISH (Fig. 1B).

Primary resistance to EGFR TKIs is defined as disease progression during the first 3 months of treatment without any evidence of objective response. Mechanisms involved in acquired resistance, such as T790M, *MET* amplification, *PTEN* loss and *ERBB2* amplification can contribute to primary resistance.[3] A recent analysis by NGS of a small series of patients with *EGFR* mutations by Zhong et al.[3] identified novel potential primary resistance mechanisms such as mutation of *TGFR1* or single-mutation patterns (cytosine spontaneous deamination). In this work, *MET* amplification was identified as one of the most frequent mechanism of primary resistance.

Our patient showed a high level *MET* amplification with a ratio >5 that probably would have contributed to a lack of response to EGFR targeted therapy. Sequential gene testing has been until recently the most common way of molecular diagnosis in patients with advanced NSCLC. This is currently being substituted by multiplex testing by NGS techniques that allows for testing of multiple

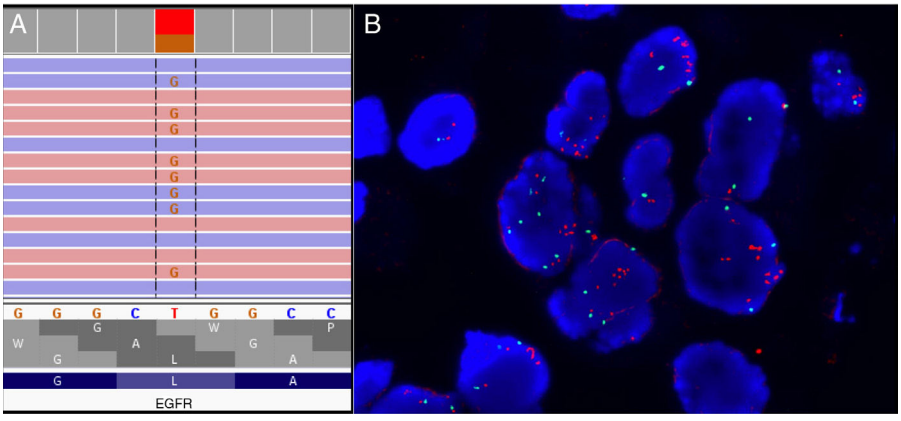


Fig. 1. (A) Liver biopsy: NGS (Oncomine Solid Tumor DNA) detects an *EGFR* mutation in exon 21. (B) Liver biopsy: *MET* FISH (Abbot Vysis Probe Kit) showing a typical amplification pattern.

genomic alterations relevant to the patient care. Our case represents one of the situations were upfront multiplex testing would have allowed a more informed decision on patient care with a more appropriate selection for the therapeutic approach.

Comprehensive genomic analysis by NGS has brought a new scenario to the lung cancer diagnostic field and will probably impact positively in the outcome of patients.

References

1. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. 2009;361:958–67.
2. Douillard JY, Ostoros G, Cobo M, Ciuleanu T, McCormack R, Webster A, et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. Br J Cancer. 2014;110:55–62.
3. Zhong J, Li L, Wang Z, Bai H, Gai F, Duan J, et al. Potential resistance mechanisms revealed by targeted sequencing from lung adenocarcinoma patients with primary resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). J Thorac Oncol. 2017;12:1766–78.
4. Westover D, Zugazagoitia J, Cho BC, Lovly CM, Paz-Ares L. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. Ann Oncol. 2018;29:i10–9.

Laura Moliner[a,*], Concepción Fernández[b], Sergi Clavé[b], Edurne Arriola[a]

[a] *Medical Oncology Department, Hospital del Mar, Barcelona, Spain*
[b] *Pathology Department, Hospital del Mar, Barcelona, Spain*

* Corresponding author.
E-mail address: lmoliner@parcdesalutmar.cat (L. Moliner).

https://doi.org/10.1016/j.arbres.2018.07.014
0300-2896/

Combined Pulmonary Fibrosis and Emphysema Versus Idiopathic Pulmonary Fibrosis Versus Emphysema: A Clinical Perspective

Comparación con perspectiva clínica de la combinación de fibrosis pulmonar y enfisema, la fibrosis pulmonar idiopática y el enfisema

Dear Editor:

Combined pulmonary fibrosis and emphysema (CPFE) was first described by Cottin et al. in 2005 as a distinct entity characterised by upper lobe emphysema and lower lobe fibrosis on high-resolution computed tomography (HRCT) of the chest resulting in preserved lung volumes and markedly impaired carbon monoxide diffusing capacity of the lung (DLCO).[1] Since then, a wide heterogeneity of radiological features of CPFE has been described and a consensual definition or a standard diagnostic algorithm has not yet been reached.[2–9] From a clinical standpoint, it is sometimes a challenge to distinguish emphysema from fibrosis and whether both conditions coexist.[10–11] Pulmonary function tests may be a useful adjunct tool in these uncertain cases. In view of that, this study aims to identify functional features that can help to distinguish CPFE from idiopathic pulmonary fibrosis (IPF) and/or emphysema.

We performed a retrospective analysis of patients with CPFE and IPF followed in an Interstitial Lung Diseases (ILDs) Outpatient Clinic between 2011 and 2016. A convenience sample of patients with emphysema attending a Chronic Obstructive Pulmonary Disease (COPD) Outpatient Clinic was obtained.

The diagnosis of CPFE and IPF was established by multidisciplinary discussion. The diagnostic criteria for IPF were applied according to the 2011 ATS/ERS/JRS/ALAT guidelines for diagnosis and management of IPF. CPFE was only considered in patients with emphysema involving at least 10% of the whole lung. The diagnosis of emphysema was established by visual assessment of HRCT.

Demographics, pulmonary function test results and evidence of pulmonary hypertension (PH) at diagnosis were reviewed from medical records. Only data regarding pulmonary function tests and echocardiograms performed up to 6 months within the baseline HRCT was included. PH was defined as a systolic arterial pulmonary pressure $\geq$ 40 mmHg plus central venous pressure on echocardiogram.

Kruskal–Wallis test was used to compare pulmonary function test results at diagnosis between groups. Statistical significance was set at $p < 0.05$.

We identified 14 patients with CPFE, 49 with IPF (35 UIP pattern; 16 possible/inconsistent UIP, who underwent lung biopsy) and 57 with emphysema. Overall, 85% were men with a median age at diagnosis of 68.5 years (IQR 61.0–75.0) and 21% were never smokers. All CPFE patients were male and all but two were current or ex-smokers. The median age at diagnosis was 66.5 years (IQR 60.8–77.0) and 30.8% of CPFE patients had PH at diagnosis. No significant differences between patients with CPFE and patients with IPF or emphysema were found regarding gender, age at diagnosis, smoking history or prevalence of PH at diagnosis.

The pulmonary function test results at diagnosis are presented in Table 1. Compared to patients with emphysema, those with CPFE had lower RV% pred (p 0.005), TLC% pred (p 0.012) and RV/TLC ratio (p 0.001), and higher FEV1% ($p < 0.001$) and FEV1/FVC ratio ($p < 0.001$; all pairwise comparisons). FVC% pred (p 0.104) and DLCO% pred (p 0.118) did not differ between the three groups of patients. No significant differences in analysed pulmonary function test parameters were found comparing patients with CPFE and IPF.

In our study, CPFE was mainly diagnosed in elderly male smokers, as previously described.[1,3,5–9,12–14] Almost a third of CPFE patients had PH at diagnosis, and this prevalence did not significantly differ in comparison with IPF or emphysema patients. However, there is previous evidence that PH is more frequent in CPFE than IPF or emphysema patients.[1,5–9,12]

To the best of our knowledge, RV/TLC ratio has not been described in CPFE, or even compared between CPFE, IPF and emphysema patients. We found that CPFE patients had significantly lower RV/TLC ratio than emphysema patients (39.8 vs. 56.8). Accordingly, a normal (lower than 40) or slightly increased RV/TLC ratio could help to discriminate patients with emphysema and superimposed fibrosis from patients only with emphysema.

CPFE patients had significantly lower static lung volumes and higher FEV1% pred and FEV1/FVC ratio compared to emphysema patients, which is in accordance with previous studies.[3,5]

A trend towards higher lung volumes was seen comparing CPFE and IPF patients, but did not reach statistical significance. Our IPF patients had median lung volumes at diagnosis within the normal or near-normal range, which could underestimate the difference between these two groups of patients. Kohashi et al. also did not find significant differences in FEV1% pred, FVC% pred and FEV1/FVC ratio between IPF alone and IPF-emphysema.[14] However, other studies have consistently shown higher lung volumes and lower FEV1/FVC ratio in CPFE versus IPF.[5,13,14]