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a Centro Hospitalar e Universitário de Coimbra, Portugal
b Centro Hospitalar São João, Porto, Portugal
c Centro Hospitalar Lisboa Norte, Lisboa, Portugal
d Instituto Português de Oncologia Francisco Gentil, Lisboa, Portugal
e Instituto Português de Oncologia Francisco Gentil, Porto, Portugal
f Centro Hospitalar Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal
g Centro Hospitalar Baixo Vouga, Aveiro, Portugal
h Roche Farmacêutica Quimica, Portugal

Corresponding author.
E-mail address: ana.antunes@roche.com (A. Antunes).

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Value of rebiopsy in advanced Epidermal Growth Factor Receptor mutated Non-Small Cell Lung Cancer: Real-world data

Letter to the Editor

Acquisition of Epidermal Growth Factor Receptor (EGFR) mutation resistance (mainly T790M) to EGFR tyrosine kinase inhibitors (TKI) occurs in about half of Non-Small Cell Lung Cancer (NSCLC) patients treated with TKI.1 Mutational status is important to guide therapy.2–4 Pirker stated that while tissue biopsy is currently the main source for molecular analyses, liquid biopsies will gain importance for diagnosis and disease monitoring in the future.5 The aim of this study was to analyse the value of liquid and tissue biopsy for evaluation of EGFR mutational status in a real-world setting.5,6

We carried out a retrospective identification of patients tested for EGFR mutation at a Portuguese cancer center between January 2015 and October 2019. We collected clinical data from patients with advanced EGFR mutation NSCLC. Descriptive statistic was used to analyse patients’ characteristics.

Of the 824 patients that were evaluated for EGFR mutation, 160 (19%) had EGFR-mutant NSCLC.
Eighty-five of 160 patients (53%) had advanced disease (11 patients with stage III, 65 patients with stage IV and 9 patients presented a relapsing NSCLC). All neoplasms were adenocarcinomas due to a selection bias of our institution (only adenocarcinomas are tested for EGFR mutation). The median age at diagnosis was 69 years old [range: 39-95] and 66% of patients were female. History of tobacco use was reported as 42%.

The most common EGFR mutation was exon 19 deletion (del19) (33 patients) followed by L858R point mutation on exon 21 (24 patients) and del19 plus de novo T790M mutation (7 patients). Other uncommon mutations identified were L858R plus T790M, G719X on exon 18, del19 plus insertion of 20 and S768I on exon 20 plus L858R.

Sixty-nine of 85 patients (81%) received EGFR-TKI and 46 patients (67%) developed disease progression on TKI. All 46 patients were submitted to a first (1st) biopsy, corresponding to a total of 50 biopsies: 25 liquid biopsies and 25 tissue biopsies/cytologies (some patients had both). Eighteen patients underwent a second and third (2nd/3rd) biopsy, corresponding to a total of 34 biopsies: 25 liquid biopsies and 9 tissue biopsies/cytologies.

The most common sampling method was liquid biopsy both for 1st (50%) and 2nd/3rd biopsies (74%). Bronchial tissue was the most common site for tissue biopsy/cytology followed by pleural fluid both in 1st and 2nd/3rd biopsies. Less common sites were cerebrospinal fluid, thoracic lymph nodes and bronchial secretions for 1st biopsy and brain and bone for 2nd/3rd biopsies.

We analysed the proportion of T790M mutation identified for each biopsy site as shown in Table 1.

As shown in Fig. 1, 16 of 46 patients (35%) undergoing a 1st biopsy harbored a T790M mutation. Among the 30 remaining patients, 12 did not repeat biopsy and 18 were submitted to a 2nd/3rd biopsy. Five of those 18 patients (28%) were submitted to 2nd/3rd biopsies harbored a T790M mutation.

Furthermore, 18 of 46 patients undergoing biopsy presented exclusive intrathoracic disease. In this setting, T790M mutation was detected in 5 of 40 all biopsies (13%).

In patients with exclusive intrathoracic disease, liquid biopsy failed to identify T790M mutation, regardless of the number of biopsies. However, out of those 20 negative liquid biopsies, one had a positive matched tissue biopsy/cytology. T790M mutation was identified in 5 of 20 tissue rebiopsies/cytologies performed (25%).

Among 28 patients with extrathoracic disease, T790M mutation was detected in 17 of 44 biopsies performed (39%). T790M mutation was found in 10 of 30 liquid biopsies (33%) and in 10 of 14 tissue biopsies/cytologies (50%).

The overall survival was higher among patients submitted to rebiopsy [28.9 months (95%CI 21.2–35.0)] than among those not [18.6 months (95%CI 9.87-NR)]. Although the increase of 10 months in overall survival was not statistically significant (p = 0.3116), this lack of significance might be related with the small number of our cohort. Additionally, we may consider that this tendency towards overall survival benefit could be related with a better performance status of the rebiopsied patients (fit to receive treatment). Also, we can hypothesize that rebiopsy might guide the physician to choose the best treatment, which would lead to a better overall survival.

Our results suggest that 2nd/3rd biopsies are worth performing, as the proportion of patients with mutation identified is still significant and have a clinical impact in therapeutic choices and prognosis. 7

T790M mutation is less identified in patients with exclusive intrathoracic disease. Liquid biopsy might not add value in this setting but tissue biopsy/cytology must be considered.

In extrathoracic disease, a higher proportion of T90M mutation was identified both in tissue biopsy/cytology and liquid biopsy. Although tissue biopsy/cytology was better than liquid biopsy, it is more difficult to perform and more invasive.

Furthermore EGFR mutant patients undergoing rebiopsy can present different resistance mechanisms, which reflects intratumoral and intertumoral heterogeneity, as well as dynamic changes in the relative populations of resistant clones over time. 8

Despite the retrospective single center nature and small sample of our study, it is the first to present rebiopsy data of EGFR mutated NSCLC patients in Portugal and it is in line with other similar studies. 9,10 Eun Kyong Goag et al. also reported a sample with a similar prevalence of EGFR mutations, with 561% in exon 19 del 34,1% in L858R or L861Q (compared with 47,8% of del19 and 34,8% in L858R in our sample) and the T790M mutation was identified in 43.9% patients with exon 19 del as the most significant factor affecting T790M mutation development (hazard ratio: 6.875, P = 0.014). Similarly, our detection rate of T790M was 44% after the first tissue rebiopsy and the T790M mutation was detected in 50% of patients with an initial del19 mutation

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Rebiopsy sites and T90M detection success rate.</th>
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<tbody>
<tr>
<td>1st biopsy site</td>
<td>Number of biopsies</td>
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<tr>
<td>Tissue biopsy/cytology</td>
<td>25</td>
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<tr>
<td>Bronchial tissue</td>
<td>13</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>8</td>
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<tr>
<td>Cerebrospinal fluid</td>
<td>2</td>
</tr>
<tr>
<td>Bronchial secretions</td>
<td>1</td>
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<tr>
<td>Thoracic lymph node</td>
<td>1</td>
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<tr>
<td>Liquid biopsy</td>
<td>25</td>
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<tr>
<td>2nd/3rd biopsy site</td>
<td>Number of biopsies</td>
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<tr>
<td>Tissue biopsy/cytology</td>
<td>9</td>
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<tr>
<td>Bronchial tissue</td>
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<td>Pleural fluid</td>
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<td>Brain</td>
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<tr>
<td>Bone</td>
<td>1</td>
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<tr>
<td>Liquid biopsy</td>
<td>25</td>
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(compared with 65% in Goag’s study) and in 26% of patients with and an initial L858R mutation (vs. 21.5%). Similarly in another Japanese study, the T790M mutation was also more frequent with an exon 19 deletion mutation (63%) than in those with a L858R mutation (38%) (p = 0.035). Prospective, multicenter studies are needed to validate these findings.

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**References**


Secondary organizing pneumonia after Varicella-Zoster virus infection: a rare association

Dear Editor,

Organizing pneumonia (OP) is a histologic pattern of the lungs' response to a wide variety of insults, including infectious, non-infectious, or no apparent reason (cryptogenic).1,2 It is usually a great mimicker showing a wide variety of signs, symptoms, and high-resolution computed tomography (HRCT) findings, which makes it a frequent differential diagnosis. The usual distribution in the HRCT is patchy, peribronchiolar with the presence of numerous buds of granulation tissue within alveoli, often involving alveolar ducts and small airways; areas of consolidation are also the characteristics of organizing pneumonia.2 Anatomopathological study is needed for final diagnosis.1,3,4 Although duration and initial symptoms depend on the underlying aetiology, OP usually presents with a several-month history of non-productive cough, low-grade fever, malaise, and shortness of breath. It is mostly seen in patients with pulmonary infection, drug reactions, transplantation, collagen vascular disease, granulomatosis with polyangiitis, after toxic-fume inhalation, e-cigarettes usage and, rarely, lung cancer of unknown primary site.1,5,6 When the underlying cause is not found, it is idiopathic and then called cryptogenic. Among the pulmonary infections, OP could be present after a bacterial, fungal, mycobacterial or even viral infection. Response to therapy is dependent on the treatment of the underlying cause but, usually, there is a good response to corticosteroid therapy with a good prognosis.3,4

We report a case of a 35-year-old male, smoker of 15 packs per year, who went to the emergency department with puriginous cutaneous eruption. Physical examination revealed vesicular cutaneous lesions, and on pulmonary auscultation a reduction of vesicular murmur and crepitations on the left hemithorax. Analysis identified respiratory failure, thrombocytopenia, hepatic dysfunction, and elevation of inflammatory parameters (C-Reactive Protein = 9.73 mg/dL (Normal < 0.5 mg/dL) with normal procalcitonin). The chest radiograph revealed bilateral opacities with air bronchogram (Fig. 1A). After the identification of epidemiological context for varicella-zoster infection (son with chickenpox), patient was admitted to hospital stay with the diagnosis of pneumonia due to Varicella-Zoster virus and medicated with intravenous acyclovir and levofloxacin for 7 days. A good clinical, analytical, and imaging response was observed (Fig. 1B). During the hospitalization, a thoracic computed tomography (CT) scan was done, showing multiple small nodules scattered in the pulmonary parenchyma, some forming small conglomerates and surrounding ground glass. They presented bilateral distribution, but predominantly in the lower lobes. The largest conglomerate measured was 15 mm in diameter and was located in the lower-left lobe. (Fig. 1C). The patient was discharged asymptomatic.

After one year, the patient returned to the emergency department with fever, odynophagia, cough, and haemoptysis, showing no changes in physical examination or blood analysis. The following thoracic CT revealed a micronodular pattern with mostly calcified nodules. In the lower right lobe, a dense 19 mm nodule with ground-glass pattern and, juxtaposed to this, other calcified 19 mm and 5.8 mm nodules were found. There was a growth of the previously reported lesion in the lower-left lobe, which measured 21 mm. (Fig. 2A).

Blood and sputum culture were negative and bronchoalveolar lavage showed no changes. CT guided biopsy of the lower left lobe lesion was performed, with anatomopathological exam revealing focal lesions of organizing pneumonia with foamy macrophages in intralveolar localization (Fig. 2B). After the exclusion of other causes of organizing pneumonia and considering the previous diagnosis of varicella-zoster pneumonia, this cause was assumed. Corticosteroid therapy was started with an initial dose of oral prednisolone of 30 mg (0.5 mg/kg) daily for 6 months. Symptoms and imaging gradually improved and, after 1 year, clinical or imaging recurrence was not observed (Fig. 2C).

The present report describes a case of OP associated with varicella-zoster infection. Hypersensitivity pneumonitis (HP) could have a very similar clinical presentation such as fever, cough, and ground glass consolidations on CT and has a high incidence among Portuguese population in contact with birds, mould, cork or isocyanates.7 However, besides an identifiable exposure history, imaging changes are usually upper lobe predominant. Despite the usually good prognosis with response to antigen avoidance, some chronic forms, mainly fibrotic, could have the same prognosis as idiopathic pulmonary fibrosis.8 As previously stated, OP is an histological pattern associated with a variety of disorders,1,4 however, OP is rare after viral infections. There are a few cases reported of influenza

R. Saúde-Conde a,*, S. Cristóvão-Ferreira a, E. Campoa b, M.T. Almodovar c

a Medical Oncology, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E., Lisboa, Portugal
b Medical Oncology, Centro Hospitalar Universitário do Algarve, Faro, Portugal
c Pulmonology, Instituto Português de Oncologia de Lisboa Francisco Gentil, E.P.E., Lisboa, Portugal

* Corresponding author.
E-mail address: rconde@ipolisboa.min-saude.pt (R. Saúde-Conde).
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