Letter to the Editor

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Concurrent EGFR mutation and ALK rearrangement in stage IV lung adenocarcinoma—a case report and a literature review

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To the Editor

EGFR mutation and ALK rearrangement were considered mutually exclusive mutations in non-small cell lung cancer. Upfront comprehensive mutation screening, like next-generation sequencing, enabled the discovery of simultaneous mutations. We describe a case of a woman with stage IV lung adenocarcinoma with 2 synchronous mutations at diagnosis, the EGFR p.(Leu858Arg) mutation, and an ALK rearrangement. The patient is on gefitinib for 16 months, maintaining this strategy currently. Co-occurrence of 2 targetable mutations is a particular challenge when choosing first-line treatment. We discuss the treatment options and results in patients with both mutations, which were generally associated with a poor prognosis in multiple studies comparing with one single mutation.

Introduction

Lung cancer is the most frequent malignancy (11.6%) and the primary cause of cancer mortality (18.4%).[1] The oncogenic drivers play a crucial role in advanced non-small cell lung cancer (NSCLC), as they might be a therapeutic target. The epidermal growth factor receptor (EGFR) mutations in exons 18 to 21 are present in the 10% to 20% caucasian population with lung adenocarcinoma, and fusion alterations involving anaplastic lymphoma kinase (ALK) are present in about 2% to 5%. EGFR mutations and ALK rearrangements should be tested in NSCLC. Currently, the broad molecular profiling system next-generation sequencing (NGS) is being adopted as the standard methodology for this issue, ideally in all patients with metastatic adenocarcinoma ab initio and other selected NSCLC patients. The NGS method permits the sequencing of multiple genes at the same time.[2,3] Historically, the genomic alterations in NSCLC were considered mutually exclusive.[4] Since 2011, there were some published case reports, showing the co-occurrence of these 2 mutations.[5–8] In this paper, we present a case report of a patient with both EGFR and ALK genetic alterations and a brief literature review.

Case report

A 75 years old female non-smoker patient with a past medical history of dyslipidaemia, thyroidectomy (benign nodules), and hysterectomy (metrorrhagia) was admitted to the Medical Oncology department in January/2019. She reported a 3-month history of progressive deterioration of performance status (PS), weight loss (18% body weight), asthenia, dyspnoea, progressive dorsal and lumbar back pain, and hospitalisation for a pulmonary embolism 2 months before. At the admission, the patient had an Eastern Cooperative Oncology Group (ECOG) PS 3. On physical exam, she had decreased breathing sounds in the left base on pulmonary auscultation and pain in dorsal and lumbar spine palpation with no neurological deficits. After the etiologic workup, a stage IV (cT2aN2M1c) lung adenocarcinoma was diagnosed with multiple bone, pulmonary, and pleural metastasis (Fig. 1). The PD-L1 expression was 5% to 10%. NGS test revealed the exon 21 p.(Leu858Arg) EGFR mutation and an ALK rearrangement (Fig. 2). Initially, dorsal and lumbar spinal cord antalgic radiation therapy was performed, zoledronic acid was started, and it was needed antalgic drug control. She started treatment with gefitinib 250 mg in February/2019. After 16 months, she maintains gefitinib with stable disease (Fig. 1), controlled symptoms, and an improvement in PS to ECOG 1. As toxicities, the patient presented a CTCAEv5 grade 1 skin erythema, grade 1 sporadic diarrhoea, and grade 1 occasional emesis.

Discussion

The presence of two or more concurrent mutations can occur in NSCLC patients, as described in this case report. Some retrospective and prospective studies, including European and Asian patients, revealed an incidence of coexisting EGFR mutation and ALK rearrangement in about 0.06% (10/17826 patients) to 1.6% (6/380 patients).[9–17]

The presence of possible tumoral heterogeneity in NSCLC with cells originating from different clones or the acquisition of other

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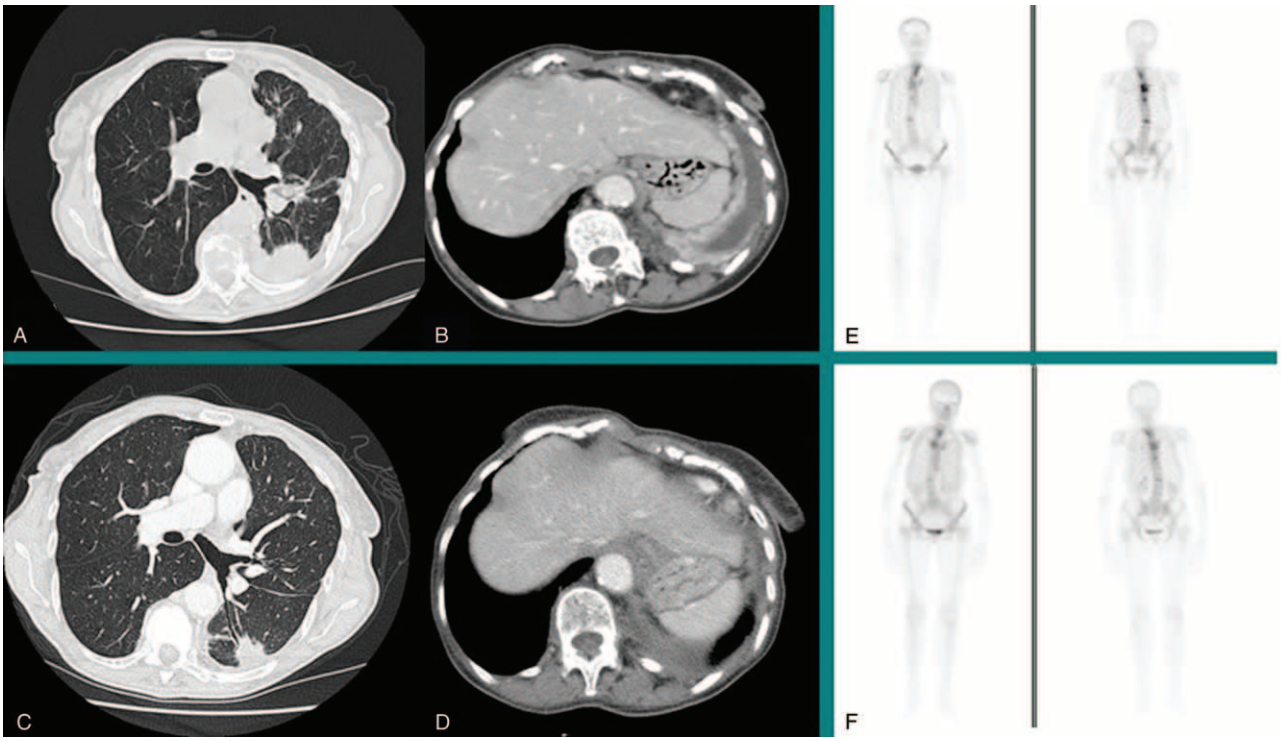

Figure 1. Baseline thoracic computed tomography (CT) scan demonstrating a 32 × 30 mm pulmonary mass in the posterior left inferior lobe and pleural metastases and pleural effusion in (A) and (B). The last thoracic CT scan image evaluation in (C) and (D) demonstrating stable disease with TKI gefitinib. Bone scintigraphy demonstrates metastatic bone disease in the spine and pelvis bone at baseline (E) and at the latest evaluation (F).

mutations due to disease progression and selective pressure by previous anticancer drugs could be detected if we used a comprehensive molecular analysis.[18] Recently, a Portuguese centre evaluated 121 NSCLC patients with at least one mutation detected by the NGS technique, and they verified that more than one mutation was identified in 21 patients.[19] NGS profiling can find additional molecular alterations that could be useful in prognostic and in treatment strategy.[20,21]

The co-occurrence of 2 targetable alterations involves a challenging task when choosing the treatment. In this case, it was a challenge to select a target for the 1st line treatment. Most of the case reports that were published included a 1st generation EGFR tyrosine kinase inhibitor (TKI) as 1st line and fewer patients treated with an ALK TKI. ALK TKI was more used as a 2nd line or beyond. The outcomes published in case reports and series of cases with both mutations have demonstrated conflicting results. A Swiss study verified that outcomes seem to be inferior in patients with ALK/EGFR co-alterations when compared to those with only an ALK translocation. The EGFR TKI was more active than ALK TKI.[22] Mao et al demonstrated that the median progression-free survival (PFS) was inferior in patients with concurrent EGFR/ALK or ROS1 (6.6 vs 10.7 months in single

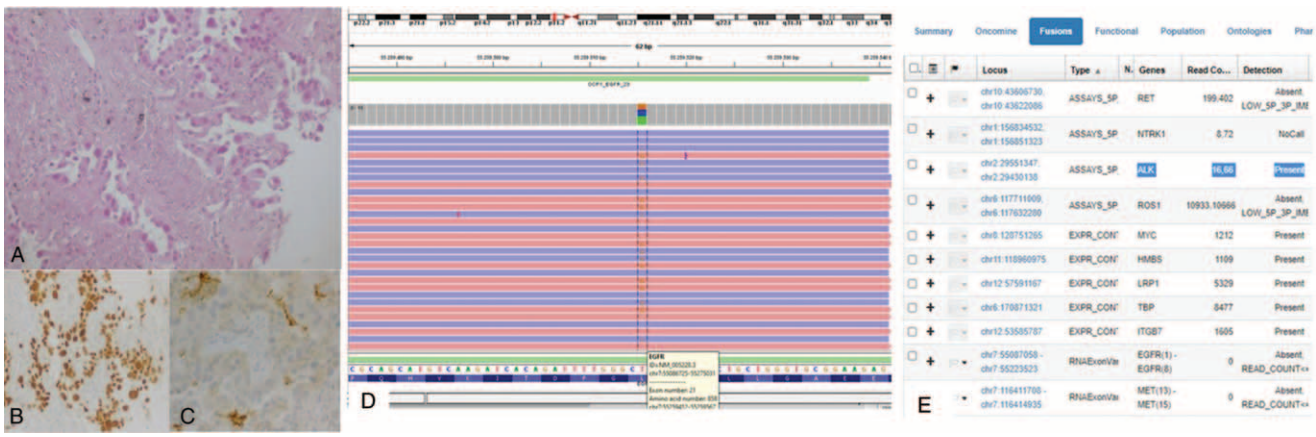

Figure 2. Histology of the primary tumour: (A) Adenocarcinoma. Irregularly shaped glands are lined by cells with abundant cytoplasm and pleomorphic nuclei (HE, 200×). (B) Diffuse TTF1 expression. (C) Focal PD-L1 expression (22C3). NGS results from the patient: (D) Presence of the exon 21 p.(Leu858Arg) EGFR mutation. (E) Presence of ALK rearrangement, along with positive control genes (MYC, HMBS, PRPI, TBP and ITGB7).

EGFR mutations, $P=.004$), with no impact on overall survival (OS).[9] In a Korean study, ALK inhibitors appeared to be effective for patients with co-alterations.[11] Ulivi et al reported discordant results in patients treated with EGFR TKI as 1st line, and a reduced response to TKI compared with patients with a single mutation, albeit not significantly.[12]

An Italian study published in 2017, the larger revision carried out on this theme, evaluated 100 patients with EML4-ALK rearrangement and EGFR mutations. Both deletions in the exon 19, p.(Leu858Arg) mutation, and some other rarer were detected. Analysing the 26 evaluable lines of therapy, they verified that the percentage of disease control was 61.5% (n=16), and the objective response rate (ORR) was 23.1% (n=6) with EGFR TKI. The proportion of disease control was 73.1% (n=19), and ORR was 42.3% (n=11) with ALK TKI.[23] In a French study, the outcomes weren't significantly different between patients with EGFR and concurrent EGFR/ALK alterations (median PFS 14.9 vs 10.3 months, $P=.23$; median OS 24.3 vs 17.7 months, $P=.94$).[14] In Wentao Hu et al study, all 6 patients were treated with 1st generation EGFR TKI with a median PFS ranging from 1.2 to 8.9 months.[15] Zhao et al published the results of 22 patients with concomitant mutations. Both 1st generation EGFR TKI and crizotinib were effective. The ORR with EGFR TKI was 63.2% (12/19) for EGFR/ALK and 62.1% (59/95) for EGFR-mutant ($P=.93$), with a median PFS of 10.3 vs 11.4 months ($P=.87$). The ORR with crizotinib was 66.7% (8/12) for EGFR/ALK and 65.0% for ALK-rearranged ($P=1.00$), with a median PFS of 11.1 vs 12.5 months ($P=.28$). Median OS was not statistically different.[16]

Our patient has a stable disease after 16 months of treatment with gefitinib in 1st line. She reached a PFS that is longer compared to most of the published case reports, that are generally associated with poorer prognosis comparing with patients with a single molecular alteration.[22]

Brigatinib causes an effective dual inhibition in both ALK rearrangements and EGFR mutations in NSCLC.[24] The use of both EGFR and ALK inhibitors could be another possible approach in these patients. A phase I study evaluated dacomitinib in combination with crizotinib after at least one previous line to overcome the problem of acquired resistance. One patient presented a partial response, and 46% had stable disease. Nearly all patients (94%) had any-grade adverse events (AEs), being 39% grade 3. The most frequent were diarrhoea, rash and fatigue. This combination of drugs was not further studied because of low efficacy and significant toxicity.[25] More data are needed in this setting.

There aren't recommendations about starting treatment with EGFR or ALK inhibitors, and both are acceptable targets. Despite the growing number of patients with concurrent EGFR/ALK changes, this number is not sufficient to generate guidelines on the choice of drugs or their sequencing.[23,26] It's crucial to understand what could be the best target to start treatment, perhaps with a comprehensive profiling test and new clinical trials.[26]

Conclusions

We described a case report of NSCLC with concurrent EGFR/ALK molecular alterations. A broad molecular characterisation allowed the discovery of multiple mutations. The use of these methodologies allows us to understand the molecular characteristics, to identify potential therapeutic targets, and to move closer to personalised medicine. Coexistent EGFR/ALK alterations can be associated with a poor prognosis and lead to some questions: what is the best treatment and sequencing? It is expected that in the future, the greater scientific and clinical knowledge using broad molecular characterisation will lead to a better definition of treatment strategies for patients with concomitant mutations, ideally guidelines by the competent entities.

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Conflicts of interest

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Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the work's integrity as a whole, and have given final approval to the published version.

Informed consent

Written informed consent was obtained from the patient.

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