



Case Report

Concomitant Rare KRAS and BRAF Mutations in Lung Adenocarcinoma: A Case Report

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Abstract: In July 2020, an active smoker, 63-year old man was admitted to the oncology unit of A.O.R.N. Sant'Anna e San Sebastiano (Caserta, Italy). Chest radiology highlighted right pleural effusion. Total-body CT scanning revealed a solid lesion with lobulated contours in the apical segment of the upper right lobe. The patient's oncologist requested a molecular assessment of EGFR, ALK, ROS1, BRAF, and KRAS, as well as an evaluation of PD-L1 expression level. To this end, we carried out NGS analysis, on DNA extracted from cytospins, by adopting a custom-designed NGS panel (SiRe®). Overall, no actionable mutations in the tested genes were identified. Conversely, concomitant BRAF exon 11 p.G469A and a KRAS exon 4 p.A146T mutations were detected. Owing to the limited data on the presence of KRAS exon 4 p.A146T point mutation in lung adenocarcinoma patients, a further molecular confirmatory analysis was carried out with a dedicated KRAS cartridge on a fully automated real time polymerase chain reaction. When DNA was extracted from the TTF-1 positive tumor cell slide, the same KRAS alteration was observed. Unfortunately, the patient died in August 2020 before having the chance to start any type of treatment.

Keywords: lung cancer; cytology; predictive molecular pathology; next generation sequencing; *BRAF*; *KRAS*

1. Introduction

Non-small cell lung cancer (NSCLC) represents the leading cause of cancer-related deaths worldwide [1]. Since the disease is mostly diagnosed in its advanced stages, cytological samples may constitute the only source of tissue material for morph-molecular purposes [2]. However, because cytological samples are often scant, it becomes highly challenging to identify the myriad of disease-associated biomarkers for therapeutic purposes. Indeed, various institutions—namely, the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), the Association for Molecular Pathology (AMP), the National Comprehensive Cancer Network (NCCN), and the American Society of Clinical Oncology (ASCO)—state that a minimum panel of genes, including Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK), ROS Proto-Oncogene 1 Receptor Tyrosine Kinase (ROS1), and V-Raf murine sarcoma viral oncogene homolog B (*BRAF*), must be tested before the administration of tyrosine kinase inhibitors (TKIs). In addition, it is required to evaluate the expression level of programmed death-ligand 1 (PD-L1) for treatment with immune-checkpoint inhibitors [3–5]. More recently, careful attention has also been paid to novel predictive biomarkers, such as Kirsten Rat Sarcoma Viral Oncogene Homolog (*KRAS*) exon 2 p.G12C, for the administration of specific TKIs

(e.g., AMG510, Amgen, Thousand Oaks, CA) [6]. Hence, to optimize the limited amount of starting tissue material for the detection of a plethora of available biomarkers, laboratories have adopted next generation sequencing (NGS), a complex yet useful tool to assess several biomarkers for different patients, simultaneously [7].

Here, we report a rare case of NSCLC featuring an unusual association of *BRAF* and *KRAS* point mutations.

2. Case Report

In July 2020, an active smoker, 63-year old man was admitted to the oncology unit of A.O.R.N. Sant'Anna e San Sebastiano (Caserta, Italy). The patient reported severe dyspnoea and 30 days of persistent dry cough. Chest radiology highlighted right pleural effusion. Total-body CT scanning revealed a solid lesion with lobulated contours in the apical segment of the upper right lobe and great post-contrastographic enhancement with a large implantation base on the anterior mediastinal pleura indissociable from its bronco-vascular structures. The solid lesion measured 36 × 22 mm. The CT analysis also confirmed a concomitant apical–basal pleural effusion measuring up to 60 mm in diameter. Such lesion caused subtotal atelectasis of the middle and right lower lobe (Figure 1A,B). In addition, pathological pericentimetric para-tracheal, pre- and sub-carinal homolateral, aortic–pulmonary, and Barety window lymphadenopathies, measuring up to 2 cm in maximum diameter, were also observed. (Figure 1C,D). No other lesions were identified in the other examined body regions.

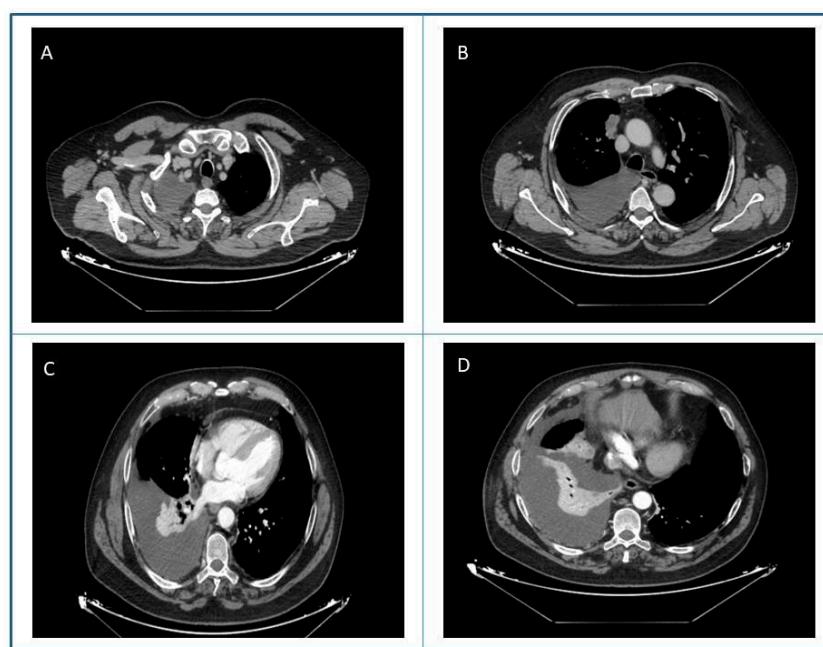


Figure 1. Radiological evaluation. (A,B) Total-body CT scanning revealed a solid lesion (36 × 22 mm) with lobulated contours in the apical segment of the upper right lobe and great post-contrastographic enhancement with a large implantation base on the anterior mediastinal pleura indissociable from its bronco-vascular structures. A concomitant apical–basal pleural effusion measuring up to 60 mm in diameter was also evaluated. As a consequence, subtotal atelectasis of the middle and right lower lobe was observed. (C,D) Pathological pericentimetric para-tracheal, pre- and sub-carinal homolateral, aortic–pulmonary and Barety window lymphadenopathies, measuring up to 2 cm in maximum diameter, were observed.

Evacuative palliative thoracentesis (about 1600 mL of bloody pleural fluid) and diagnostic bronchoscopy with biopsy of lymph node station number seven were performed. The cytological picture displayed atypical epithelial cells with severe nuclear abnormalities organized in glandular structures, as evidenced in H&E stained cytopspins (Figure 2A,B). Immunocytochemical (ICC) analysis

highlighted a strong positivity for thyroid transcription factor 1 (TTF-1) and negativity for calretinin and Wilms tumor protein (WT1); cytokeratin 7 (CK7) staining was not contributive (Figure 2C,D). Overall, on the basis of these clinical, radiological, morphological, and immunocytochemical features, a diagnosis of NSCLC favor adenocarcinoma was made.

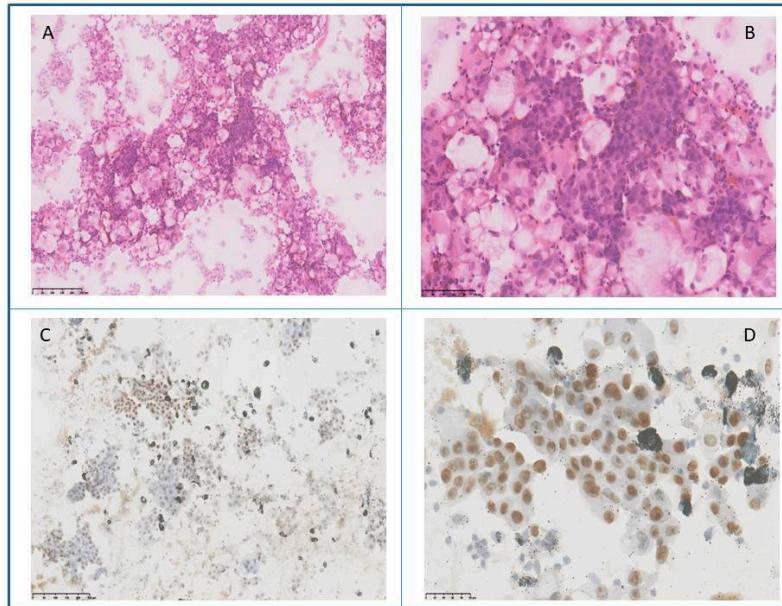


Figure 2. Cytological evaluation. **(A,B)** The cytospins cytological picture displayed atypical epithelial cells with severe nuclear abnormalities organized in glandular structures. **(C,D)** Immunocytochemical analysis highlighted a strong positivity for thyroid transcription factor 1 (TTF-1). On the basis of these morphological and immunocytochemical features, a diagnosis of non-small cell lung cancer (NSCLC) favor adenocarcinoma was made.

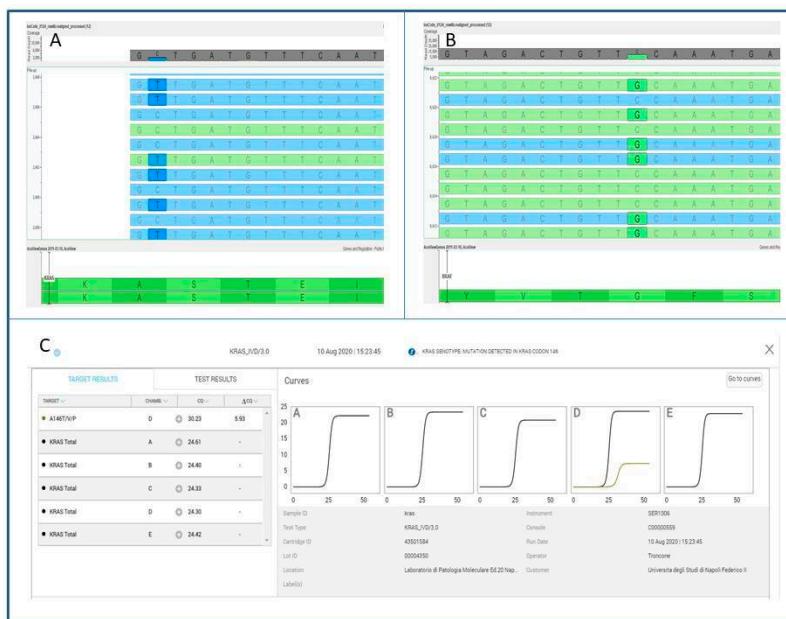


Figure 3. Molecular evaluation. **(A,B)** Next generation sequencing analysis revealed concomitant *BRAF* exon 11 p.G469A (allelic frequency 42.9%) and *KRAS* exon 4 p.A146T (allelic frequency 31.9%) mutations. **(C)** A further molecular analysis was carried out with a dedicated *KRAS* cartridge on a fully

automated real time polymerase chain reaction platform (IdyllaTM, Biocartis, Mechelen, Belgium), confirming the same *KRAS* alteration.

Following the above mentioned guidelines, the patient's oncologist requested a molecular assessment of *EGFR*, *ALK*, *ROS1*, *BRAF*, and *KRAS*, as well as an evaluation of PD-L1 expression level. To this end, we carried out NGS analysis, on DNA extracted from cytospins, by adopting a custom-designed NGS panel (SiRe[®]), developed and validated by the Predictive Molecular Pathology Laboratory of the University of Naples Federico II. This panel is able to detect 568 clinically relevant mutations in the following six genes: *EGFR*, *KRAS*, Neuroblastoma RAS Viral Oncogene Homolog (*NRAS*), *BRAF*, Platelet Derived Growth Factor Receptor Alpha [*PDGFRA*], and KIT Proto-Oncogene, Receptor Tyrosine Kinase (*KIT*) [8–13]. The analysis was performed on the Ion Torrent S5 (ThermoFisher Scientific, Waltham, MA) platform. Overall, no actionable mutations in the tested genes were identified. Conversely, concomitant *BRAF* exon 11 p.G469A (allelic frequency 42.9%) and a *KRAS* exon 4 p.A146T (allelic frequency 31.9%) mutations were detected (Figure 3A,B). Owing to the limited data on the presence of *KRAS* exon 4 p.A146T point mutation in lung adenocarcinoma patients, a further molecular confirmatory analysis was carried out with a dedicated *KRAS* cartridge on a fully automated real time polymerase chain reaction (RT-PCR) platform (IdyllaTM, Biocartis, Mechelen, Belgium) [14]. When DNA was extracted from the TTF-1 positive tumor cell slide, the same *KRAS* alteration was observed (Figure 3C). Unfortunately, the patient died in August 2020 before having the chance to start any type of treatment.

3. Ethical Statement

Written informed consent was obtained from the patient and documented in accordance with the general authorization to process personal data for scientific research purposes from 'The Italian Data Protection Authority' (<http://www.garanteprivacy.it/web/guest/home/docweb/-/docwebdisplay/export/2485392>). All information regarding human material was managed using anonymous numerical codes, and all samples were handled in compliance with the Declaration of Helsinki (<http://www.wma.net/en/30publications/10policies/b3/>).

4. Discussion

Here, we report a rare case of lung adenocarcinoma harboring concomitant *KRAS* exon 4 p.A146T (COSM19404) and *BRAF* exon 11 p.G469A (COSM460) point mutations. To the best of our knowledge, although *KRAS* and *BRAF* co-occurring mutations have already been described in the literature, no study has ever reported the co-occurrence of these two rare genomic events in NSCLC patients.

Typically, *KRAS* mutations are found in 25–30% of NSCLC patients, in particular in Western countries and in smokers [15]. Up to 90% of *KRAS* mutations are found in codon 12 (exon 2), and, in particular, in p.G12C and p.G12V, due to G:C to T:A transversion in smokers [16]. Preliminary studies from early clinical trials have indicated that although these mutations are associated with negative prognoses, *KRAS* exon 2 p.G12C mutations, which account for about 13% of NSCLC patients, have acquired a relevant positive predictive significance as actionable biomarker [17]. On the other hand, *KRAS* exon 4 p.A146T is a very rare event in NSCLC adenocarcinoma patients (0.08%) [18]. This mutation seems to be associated with elevated expression levels of both RAS-GTP and extracellular signal-regulated kinase (ERK) compared with wild-type RAS cells. Therefore, *KRAS* exon 4 p.A146T is considered an activating missense mutation [19,20]. Recently, Wang et al. further confirmed the very rare occurrence of *KRAS* exon 4 p.A146T (0.41%) in the metastatic lung adenocarcinoma setting [21]. Not surprisingly, *KRAS* exon 4 p.A146T point mutation plays a negative predictive role when EGFR TKIs are administered [22].

As opposed to *KRAS* mutations, *BRAF* mutations have a lower incidence, occurring in only 1.5–3.5% to 7–8% of NSCLC patients. They are typically associated with micropapillary adenocarcinoma histotype, and with current and former smokers [23]. Discordant results have however been reported

on the prevalence of *BRAF* exon 15 p.V600E and non-p.V600E alterations [24–26]. Similar to *KRAS* exon 4 p.A146T point mutation, the occurrence of *BRAF* exon 11 p.G469A is reported in a low percentage of lung adenocarcinomas (0.42%) [18]. To date, some studies indicate that only *BRAF* exon 15 p.V600E point mutation may predict the response to the combination of dabrafenib (*BRAF* inhibitor) and trametinib (MEK inhibitor) [27,28]. By contrast, other studies have highlighted the sensitivity of *BRAF* non-p.V600 point mutations, including *BRAF* exon 11 p.G469A, to this drug combination [26].

As of today, the co-occurrence of *KRAS* and *BRAF* mutations in lung adenocarcinoma is not well established. In a large experience, the Lung Cancer Mutation Consortium evidenced the occurrence of *BRAF* mutations with other concomitant oncogenic drivers (including *KRAS*) in a limited number of patients (5%) [29]. Salimian et al. reported concomitant *KRAS* and *BRAF* alterations in only 11% of analyzed cases [25]. Interestingly, in our present case and in a previous experience [24], we found that all cases with a concomitant *KRAS* mutation harbored a *BRAF* non-p.V600E alteration [25]. Similarly, another study has reported activating *KRAS* mutations in 11 (18%) out of 63 *BRAF* mutated patients [30]. Of note, all cases featured a *BRAF* non-p.V600E point mutation. Furthermore, two harbored a *KRAS* exon 4 p.A146T with a *BRAF* exon 11 p.G466V or *BRAF* exon 15 p.K601N [30]. As far as treatment is concerned, Gautschi et al. highlighted that the co-existence of *KRAS* exon 2 p.G12V with a *BRAF* exon 15 p.V600K determined the resistance to *BRAF* TKI treatments [31]. However, novel therapeutic approaches are under investigation for these patients. Interestingly, promising results have been reported in both *RAS* and *BRAF* mutated cell lines and in phase I dose-escalation and expansion studies of two novel molecules, ulixertinib (ERK1/2 kinase inhibitor) and LY3009120 (pan-*RAF* inhibitor) [32,33].

In conclusion, this is the first report describing the association of two rare mutations in *KRAS* and *BRAF* (*KRAS* exon 4 p.A146T and *BRAF* exon 11 p.G469A) in a lung adenocarcinoma patient. In this experience, our custom-designed NGS panel enabled us to run a successful genetic testing despite having scant cytological material. Nonetheless, even though custom-designed NGS yield accurate data, we recommend that orthogonal methodologies should be implemented to guarantee the accuracy of very rare molecular events, such as the *KRAS* exon 4 p.A146T point mutation. Finally, one limitation of this case report is that, unfortunately, our patient died before he could benefit from a personalized treatment plan. Consequently, further studies will be needed to better define the role of these co-occurring mutations in the hope of designing personalized treatment strategies for advanced stage NSCLC patients.

Author Contributions: Conceptualization, A.I. and U.M.; Methodology, all authors; Software, all authors; Validation, all authors; Formal Analysis, all authors; Investigation, all authors; Resources, all authors; Data Curation, all authors; Writing—Original Draft Preparation, all authors; Writing—Review & Editing, all authors; Visualization, all authors; Supervision, U.M.; Project Administration, U.M. All authors have read and agreed to the published version of the manuscript.

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