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Case Report
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Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) with a Rare Epidermal Growth Factor Receptor (EGFR) Mutation Treated with Osimertinib

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Introduction

Mutation in codon 747 from leucine to proline; c.2239_2240delinsCC, p.(Leu747Pro) of exon 19 in the Epidermal Growth Factor Receptor (EGFR) gene in advanced Non-Small Cell Lung Cancer (NSCLC) is very rare, therefore the activity of Tyrosine Kinase Inhibitors (TKIs) are not conclusive. We report a case treated with first line Osimertinib and a review of what has been reported on the limited cases with this rare gene alteration.

Case Presentation

A 75-year-old white male, former smoker (15 peaks/year), for worsening of dyspnea referred to first aid where a chest X-ray showed massive pleural effusion.

Afterwards a total-body CT-scan showed a pulmonary lesion in upper left lobe, multiple pleural thickenings by metastatic plaques and enlarged omo- and contro-lateral mediastinal lymph-nodes (Figure 1).

Patient underwent to exploratory thoracoscopy: thoracic surgeon found important pleural involvement by multiple metastatic plaques which were biopsied. Surgery concluded with drainage of a total of 3 liters of serum-hematic fluid, positioning of pleural drainage and talcing of the pleural cavity. Histologic exam reveals parietal pleural localization of adenocarcinoma with a papillary growth pattern coherent with pulmonary origin, for and overall staging disease of cT3cN3M1a.

PD-L1 level expression was performed in automation (BenchMark ULTRA) by DAKO PD-L1 antibody (clone 22C3) showing a low-level expression (4%).

Tissue sections were macrodissected, to enrich the tumor content, prior to DNA and RNA isolation; the macrodissected area was estimated to contain approximately 70% neoplastic cells.

DNA and RNA have been extracted by Maxwell RSC DNA and RNA FFPE Kit (Promega, Madison, WI, USA), following the manufacturer's protocol. DNA and RNA concentrations were determined by fluorometric quantitation using a Qubit 4.0 Fluorometer with Qubit DNA dsDNA HS Assay Kit and Qubit RNA HS Assay Kit (Thermo Fisher), as appropriate.

To estimate somatic mutation profiling, NGS was performed with the "Ion Torrent Oncomine Focus Assay" for simultaneous and rapid identification of Single-Nucleotide Variants (SNVs), short insertion and deletions (indels; 35 genes), CNVs (19 genes), and gene rearrangements (23 genes) in 52 cancer genes with therapeutic relevance: Hotspot genes (35): AKT1, ALK, AR, BRAF, CDK4, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ESR1, FGFR2, FGFR3, GNA11, GNAQ, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, PDGFRA, PIK3CA, RAF1, RET, ROS1, and SMO. CNV genes (19): ALK, AR, BRAF, CCND1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, FGFR4, KIT, KRAS, MET, MYC, MYCN, PDGFRA, and PIK3CA. Fusion driver genes (23): ABL1, ALK, AKT3, AXL, BRAF, EGFR, ERBB2, ERG, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, MET, NTRK1, NTRK2, NTRK3, PDGFRA, PPARG, RAF1, RET, and ROS1.

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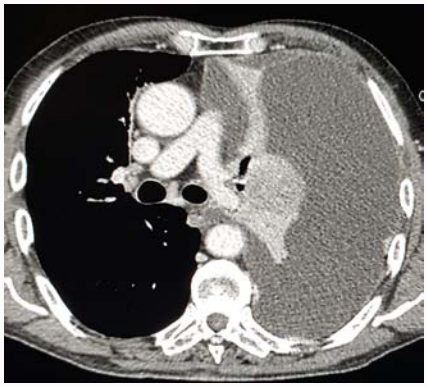

Figure 1: CT scan staging disease.

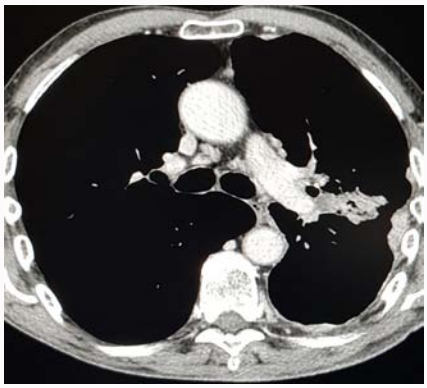

Figure 2: Restaging following three months of Osimertinib.

The Invitrogen SuperScript™ VILO™ cDNA Synthesis Kit (Thermo Fisher Scientific) was used for RNA reverse transcription to cDNA before library preparation. Libraries were prepared from 10 ng DNA and 10 ng RNA (0.67 ng/µl, 15 µl) with "Oncomine Focus Assay, Chef-Ready Library" reagents on the Ion Chef™ System (Thermo Fisher Scientific). Templating and sequencing were performed using "Ion 510™ & Ion 520™ & Ion 530™ Kit–Chef." For template preparation, we used Ion 520 chip (up to 5 million reads per chip, 8 samples) on the Ion Chef™ System, while sequencing was completed on the Ion Torrent S5 Plus (Thermo Fisher Scientific). Sequencing data were analyzed using Ion Reporter™ Software that helps to identify and prioritize variants. To define a reliable variant calling, we have considered two stringent parameters: Coverage depth greater than 500× and allele frequency greater than 5%.

Instead of the expected deletion the sequencing traces showed a 2 bp indel causing an amino acid substitution at codon 747 from leucine to proline; c.2239_2240delinsCC, p.(Leu747Pro). No other genetic alterations have been found.

Patient received Osimertinib fist-line therapy: Treatment was well tolerated with no significant side effect yielding at the same time an improvement of overall quality of life.

About three months later patient underwent to restaging: CEA tumor marker decrease from 698 to 461 whereas a total body CT scan confirm the presence of left pulmonary lesion (Figure 2), unchanged the ilo-mestastinal lymph nodes and no pleural effusion, no metastatic lesions in the abdominal, bone and cerebral districts were reported.

Patient continued Osimertinib for other three months: Therapy was well tolerated but he had a progressive worsening of dyspnea.

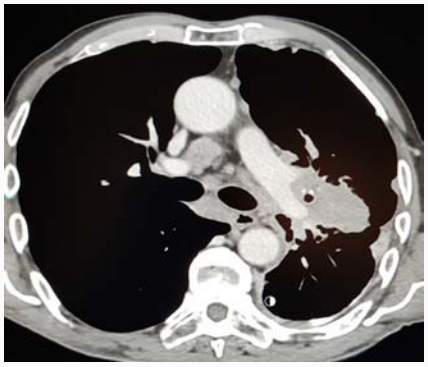

Figure 3: Restaging following six months of Osimertinib.

Restaging exams included CEA, enhanced to 556, and total body CT scan that showed thoracic progression disease (Figure 3) with new metastatic lesions to bones, lymph nodes and spleen.

An enlarged lymph node in left axilla was surgical removed: Histologic exam revealed massive metastasis from adenocarcinoma with papillary architecture with pulmonary primitiveness.

Tissue sections were macrodissected and the selected area was estimated to contain approximately 90% neoplastic cells; DNA and RNA extracted confirmed the same biologic and mutation known.

Mutational analysis was performed by the amplicon-based NGS panel "Myriapod NGS Cancer panel DNA and RNA CE-IVD" (Diatech Pharmacogenetics) on the MiSeq platform (Illumina). This panel allows investigation of a total of 107 DNA regions involving the hot-spot regions of 16 distinctive cancer related genes (ALK, BRAF, EGFR, ERBB2, FGFR3, HRAS, IDH1, IDH2, KIT, KRAS, MET, NRAS, PDGFRa, PIK3CA, RET and ROS1) and the identification of gene fusions in 9 clinical diagnostic genes (ALK, ROS1, RET, NTRK1, NTRK2, NTRK3, FGFR2, FGFR3, PPARG) and the detection of skipping of exon 14 of MET. Samples DNA and RNA were amplified in two steps following the manufacturer's instructions: PCR1 was performed to amplify hot-spot regions and PCR2 was performed to provide the indexed fragments. Finally, libraries were diluted at 12 pM and pooled together for template generation. The sequencing phase was performed on the MiSeq platform (Illumina) according to the manufacturer's instructions.

Data analysis for coverage and variant calling inspection was carried out by Myriapod NGS Data analysis Software V.5.0.4 (Diatech Pharmacogenetics). In detail, samples with minimal coverage of 500× and a variant alteration of ≥ 5% were selected.

Once again NGS confirmed the same biological profile showed in the first analysis.

Nearly to begin a rescue systemic therapy, patient had an ischemic cerebral stroke with worsening of performance score and for this reason referred to palliative care.

Clinical information regarding the c.2239_2240delinsCC p.(Leu747Pro) mutation is very limited with a dozen cases identified in the Catalogue of Somatic Mutations in Cancer (COSMIC) (http://cancer.sanger.ac.uk/ cancergenome/projects/cosmic/).

In 2014 Walsh et al. [1] published a poor prognosis case report with the same biologic characteristic: The authors suspected that the

commercially available kit used does not have sufficient accuracy to recognize the real mutations present in the genomic profile of the disease; probably the erroneous detection of an exon 19 deletion with the Therascreen and COBAS kits is presumed to be caused by miss-priming of PCR oligonucleotides.

In contrast to Walsh et al. experience, we obtained two histologic samples at baseline and progression disease where tumor cell representation was very high and both the genetic profiles confirmed the existence of this rare mutation.

Nevertheless, activity of first or second generation TKIs, such as gefitinib or erlotinib, in presence of this rare biomarker is unclear: There were two progressive diseases [2] one stable disease [3] and one partial response in a second-line setting [4]; in our experience we yielded a disease control of six months with first-line third generation TKIs (Osimertinib) confirming that the clinical implications in this rare setting of TKIs are not well known.

Conclusion

Further experiences are needed in patients with this rare mutation, in order to better characterize the predictive and prognostic behavior, and consequently to be able to affirm if TKIs also in these rare cases might be the optimal therapy to offer as first-line therapy.

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