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Carving out another slice of the pie: Exceptional response to single agent imatinib in an asian female never-smoker with advanced NSCLC with a de-novo PDGFR-α N848 K mutation

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ABSTRACT

Non-small cell lung cancer (NSCLC) has emerged as a paradigm for clinical application of precision medicine as optimal therapy is commonly chosen based on genomic biomarkers identified in a patient's tumor sample. Recurrent driver alterations are well described, however, a need to continually identify rare variants remains clinically relevant. We identified an incident case of advanced NSCLC with a PDGFR-α N848 K activation loop mutation with no other concurrent oncogenic drivers. Amino acid sequence alignment confirmed homology to the imatinib-sensitive KIT N822 K activation loop mutation observed in GIST. The patient achieved a 2-year response to single agent imatinib that is ongoing. While PDGFR-α N848 K is rare among public sequencing databases our cases strongly suggests functional relevance and highlights the importance of studying rare variants in NSCLC.

1. Introduction

Advances in DNA and RNA sequencing have redefined tumor classification, shifting the paradigm towards molecular characterization to inform systemic treatment strategies. Non-small cell lung cancer (NSCLC) has emerged as a paradigm for clinical application of precision medicine as optimal therapy is commonly chosen based on genomic biomarkers identified in a patient's tumor sample. Next-generation based genomic profiling has identified uncommon alterations in NSCLC, most recently highlighted by *MET* exon 14 skipping, *NTRK1* re-arrangements, and *HER2* transmemberane domain (TMD) mutations [1]. Large scale comprehensive molecular profiling of 860 cases of lung adenocarcinomas has identified numerous actionable driver mutations; however, up to 12% of the lung adenocarcinoma have no actionable mutations identified [2].

The platelet-derived growth factor receptor alpha (PGDFR-α) is one of 58 human receptor tyrosine kinases and belongs to one of 20 sub-families that also include KIT, PDGFR-β, macrophage colony stimulating-factor receptor (CSF1R) and Fl cytokine receptor (FLT3). Mutually exclusive from KIT, activating PDGFR-*α* alterations in the ATP-binding domain, juxtamembrane domain, or the activation loop are established driver mutations in gastrointestinal stromal tumors (GIST) [3]. While some PDGFR-*α* alterations arise in the context of imatinib resistance in GIST, the majority are de-novo and sensitize to imatinib treatment. In GISTs, alterations in exon 18, encoding the activation loop of the second tyrosine kinase domain, account for over 80% of *PDGFRA* alterations, and corresponding exon 17 *KIT* alterations are rare. Outside of GISTs, the relationship between *PDGFRA* mutation and imatinib responsiveness is not well-studied, and unselected trials of imatinib in NSCLC have been negative [4,5]. Herein, we describe the first reported PDGFR-α N848 K activation loop mutation in NSCLC and demonstrate a highly durable response to single agent imatinib.

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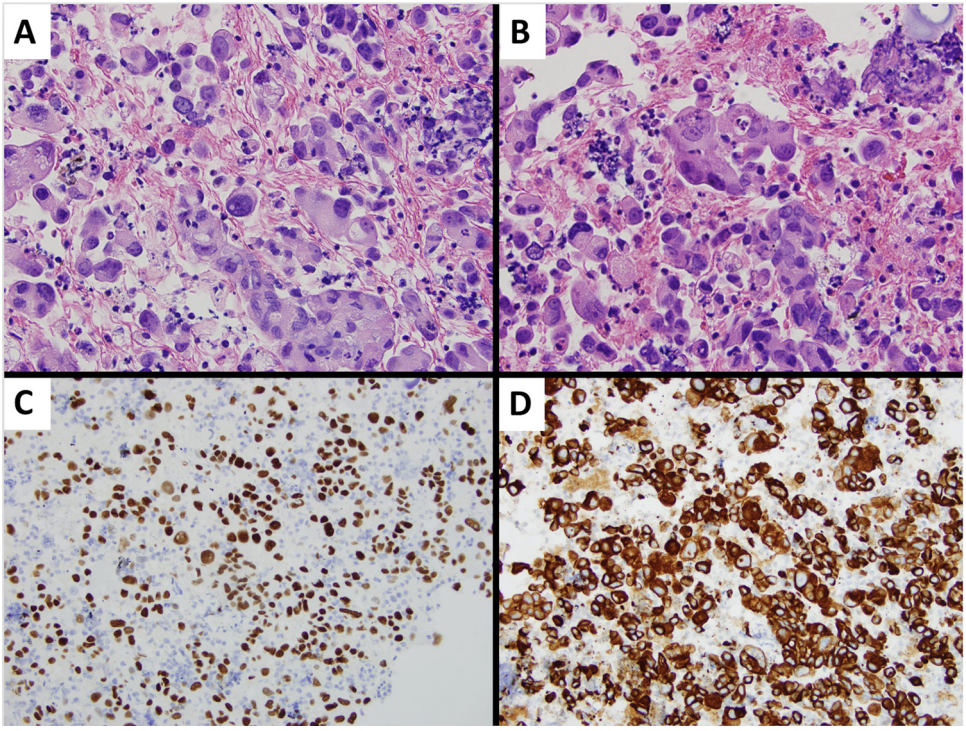

Fig. 1. Cell block from endobronchial ultrasound guided fine needle aspirate of station 7 lymph node showing poorly differentiated carcinoma with rare intracellular mucin (panels A–B). Immunostains performed are positive for TTF1 (C) and CK7 (D), consistent with poorly differentiated adenocarcinoma of the lung.

2. Case report

A 43-year-old Asian female never-smoker presented with persistent cough and was diagnosed with stage IV NSCLC when she underwent computed tomography (CT) and positron emission tomography (PET) imaging that revealed a FDG-avid 3.4 cm left upper lob mass (LUL), a 1.2 cm left lower lobe mass, multiple pleural-based LUL lesions, and FDG-avid borderline mediastinal adenopathy. Bronchoscopic sampling of a subcarinal lymph node was positive for poorly differentiated adenocarcinoma, positive for CK7 and TTF1 consistent with a primary non-small cell lung cancer (Fig. 1A–D). At diagnosis her biopsy sample was submitted for comprehensive genomic profiling (CGP; FoundationOne, Foundation Medicine, Inc.) and found to harbor a PDGFR-α N848 K mutation at an estimated mutant allele frequency (MAF) of 22%. There were no alterations in other putative or established oncogenic NSCLC drivers and the overall tumor mutational burden (TMB) was 2 mutations per DNA megabase (MB) (Supplemental table 1). Given there had been no reported PDGFR-α N848 K mutations in lung cancer literature she began on first line carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab maintenance therapy. She achieved a partial response by RECIST v1.1 and continued on therapy for a total of 12 months when she developed a new FDG-avid aortocaval lymph node (Fig. 2). A relevant clinical trial was not available, and in light of her preference to avoid further chemotherapy or immunotherapy she was started on a trial of second line single agent imatinib, 400 mg orally once per day after informed consent. She tolerated therapy well and CT of the chest four weeks after starting therapy showed a decrease in size of her dominant LUL mass (Fig. 2). Subsequent PET-CT 3 months after starting therapy showed a 41% decrease in FDG-uptake in the LUL mass and resolution of the FDG-avid aortocaval lymph node (Fig. 2). She had minimal side effects from imatinib with no myelosuppression, peripheral or periorbital edema. After 12 month response on imatinib she developed a slight increase in size of the aortopulmonary (AP) window lymph nodes with no change in the primary. After careful discussion and review of all treatment options with the patient, the decision was made to resect the primary tumor and the AP window lymph node, rendering her without evidence of disease. Pathology of the left upper lobe primary revealed poorly differentiated lipedic dominant adenocarcinoma similar to original morphology. All three resected AP window nodes were positive for metastatic disease. Additional immunohistochemistry demonstrated moderate PDGFR-α staining (Fig. 3A–D). Repeat CGP from the an AP window node was performed to assess for putative resistance mechanisms, or absence therof. CGP showed persistent PDGFR-α N848 K (MAF 9.8%) with no other putative drivers or established PDGFR-α or KIT imatinib resistance mutations (Supplemental table 1). She resumed imatinib 400 mg after surgery and completed thoracic radiation and continues to do well, now over 23 total months on imatinib with no current evidence of disease.

3. Methods

3.1. Comprehensive genomic profiling

Following pathologic confirmation, hybrid-capture based next generation sequencing was performed on lung cancer specimens submitted during routine clinical care using previously published methods. Tumor mutational burden (TMB) was determined on 1.1 Mbp of sequenced DNA, as described previously.

3.2. PDGFR-α genomic alterations

We explored the genomic context of *PDGFRA* in publicly available genomic sequencing data across solid tumors. The Cancer Genome Atlas (TCGA) and the catalog of somatic mutations in cancer (COSMIC) were accessed through the MSKCC cbioportal (www.cbioportal.org), and the COSMIC portal (http://cancer.sanger.ac.uk/cosmic) as described. *PDGFRA* exon 18 (ENSE00003570052, codons 814–854) and *KIT* exon 17 (ENSE00001074435, codons 788–828) alterations were abstracted and recorded. Known activating alterations were recorded and imatinib sensitivity or resistance was reported when available from published literature.