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Case Report

BRAF^{V600} mutant non-small-cell lung cancer resistant to Vemurafenib

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Abstract: Vemurafenib has shown significant activity in V600 mutant melanoma; however the role of this agent in Lung adenocarcinoma with an activating BRAF mutation is still evolving. One of our patients had a rare activating BRAF mutation detected through tumor exome sequencing, which led to a switch from her successful therapy to Vemurafenib and ultimately tumor progression. The lack of adequate response was disappointing both in terms of lost disease free survival and heavy financial burden to the patient who had to cover the charges of her unsuccessful off-label therapy. This experience, despite its highlight of treatment failure, puts into question the use of next generation sequencing and the trend for using off-label agents in pursuit of an optimal response without the support of strong clinical evidence.

Keywords: Lung Adenocarcinoma, BRAF mutation, Vemurafenib, next generation sequencing

Introduction

Treatment of Non-Small-Cell Lung Cancer (NSCLC) traditionally consisted of platinum-containing chemotherapy regimens, which provide an improvement in survival and palliate disease related symptoms. More recently, molecular biology has allowed for the introduction of targeted therapy into the treatment paradigm of this disease [1, 3]. In light of the advances achieved in the field of expanded mutational analysis by next generation sequencing, we present the case of a patient we treated with vemurafenib after she was diagnosed with NSCLC harbouring a rare BRAF^{V600} mutation.

Case report

A 73 year-old female, never-smoker, was referred to our oncology department in July 2013 for stage IV NSCLC.

At presentation, the patient had progressive shortness of breath and fatigue. Chest computed tomography (CT) showed a 26-millimeter nodule of the central region of the right lung with mediastinal lymph node metastasis and massive right pleural effusion. Immunohistochemistry (IHC) of the drained pleural fluid and histological examination of transbronchial biopsies confirmed the diagnosis of poorly differentiated adenocarcinoma of the lung that was positive for CK7 and TTF-1 and negative for CK5/6.

Additionally, [18F] fluorodeoxyglucose positron emission tomography (PET)/CT scan showed intense metabolic activity in the right pleura with pleural based active thickenings, an 18-millimeter hypermetabolic nodule located in segment VII of the liver and multiple sites of hypermetabolic osteo-sclerotic lesions diffusely scattered along the skeleton.

Brain magnetic resonance imaging revealed a 22×12-millimeter contrast enhancing lesion of the left frontal lobe compatible with brain metastasis. Polymerase Chain Reaction (PCR) evaluation was negative for Epidermal Growth Factor Receptor (EGFR) mutation (Exon 18, 19, 20, 21). Fluorescent in situ Hybridization did not show anaplastic lymphoma kinase rearrangement.

At the time of diagnosis, the patient scored one on the Eastern Cooperative Oncology Group Performance Status (ECOG-PS). She received 6

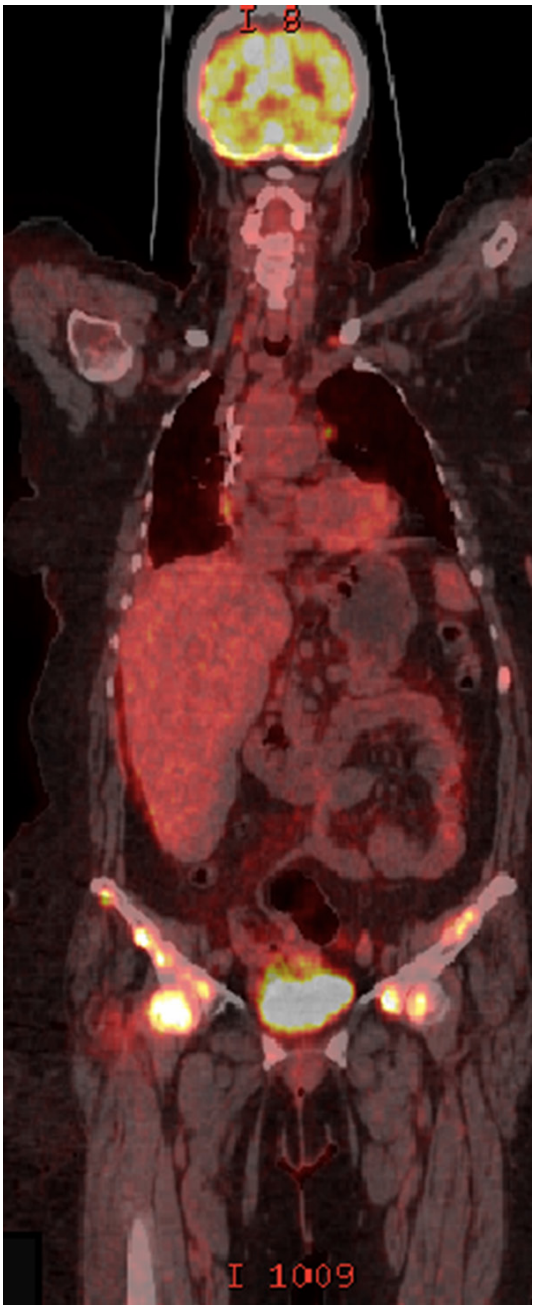

Figure 1. PET/CT scans showing metastatic Lesions before Vemurafenib Therapy.

cycles of chemotherapy with carboplatin, pemtrexed and zoledronic acid and had partial response with 30% reduction in the size of measurable lesions. Subsequently, four cycles of continuation maintenance therapy with pemetrexed were delivered. Reassessment imaging showed progression of her disease.

A CT Guided biopsy from her liver metastasis was sent for expanded mutational analysis by next generation sequencing in January 2014 revealing an activating mutation in the BRAF gene with BRAF^{V600}_K601delinsE mutation (**Figure 1**).

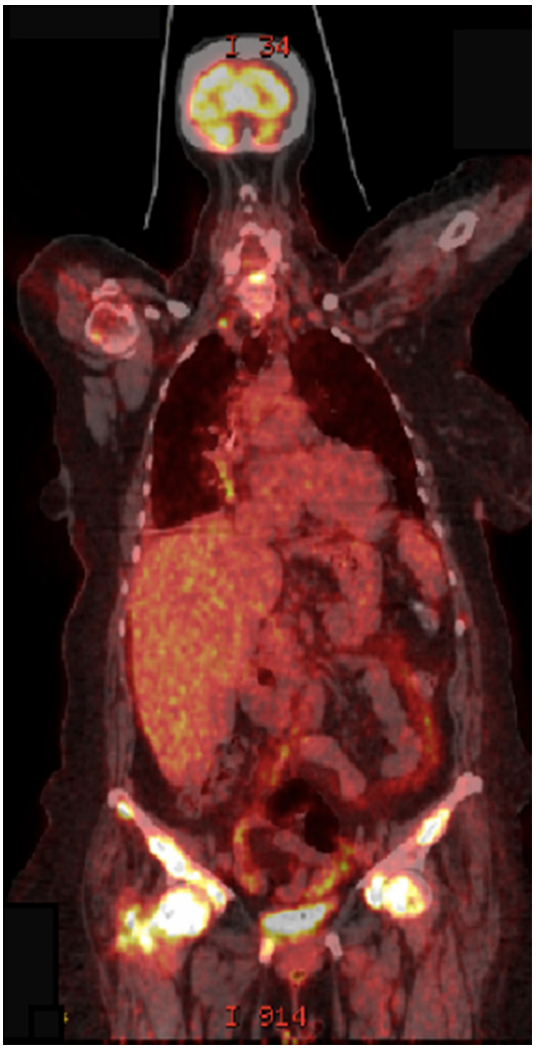

Figure 2. PET/CT scans showing progression of disease while receiving Vemurafenib Therapy.

The potential benefit of using off label Vemurafenib was discussed with the patient in lengths. The agent was started in March 2014 at a dose of 960 mg, to be taken twice daily.

Unfortunately, the patient underwent a PET/CT in June 2014 that showed progression of the secondary lesions involving the mediastinal adenopathies, right pleura, posterior wall of right hypochondrium and skeleton, thus indicating treatment failure (**Figures 2** and **3**).

Discussion

Treatment paradigms of NSCLC have historically relied on tumor histology. Further advanc-

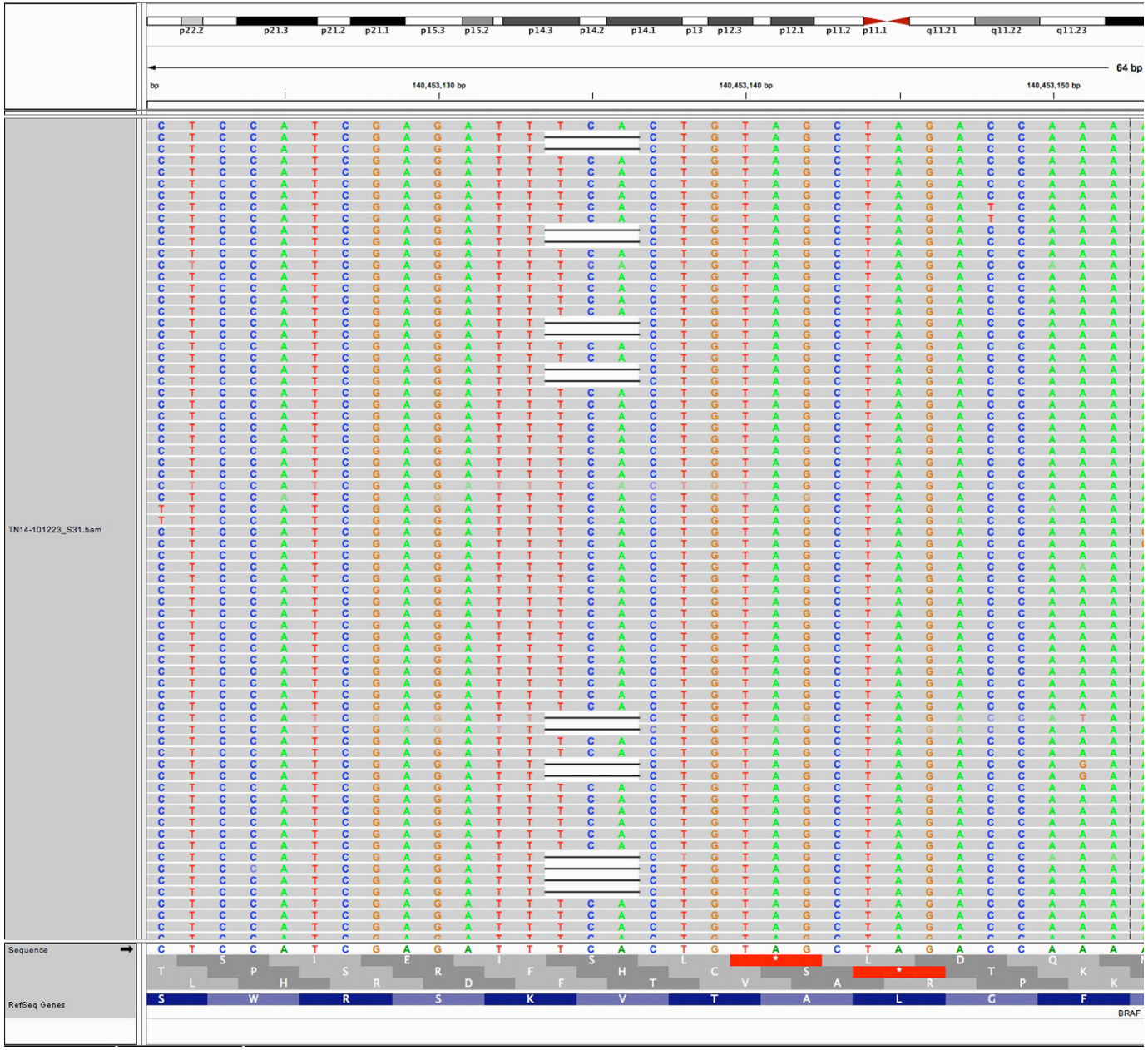

Figure 3. BRAF mutation analysis of our patient.

es over the past decade led to a paradigm shift when specific activating mutations in the Epidermal Growth Factor Receptor (EGFR) were successfully inhibited, resulting in a significant survival benefit [2].

A newer so-called "diver mutation", which has recently been shown to be important in Melanoma, was discovered in NSCLC. Mutations in the BRAF gene, with a Glutamine for a valine at residue 600 (V600E) is the most common variant and seems to have the most relevant therapeutic implications [3, 4].

Genotyping of NSCLC has shown that 3 to 5% of tumors harbor a BRAF mutation, 50% of which being a V600E mutation [5]. Some mutations in the BRAF gene seem to be more complex than others, with one being of particular interest in our patient. This mutation is comprised of one nucleotide substitution at position 1798, followed by an in-frame insertion of three nucleotides, c.1798 delinsTACA in exon 15, resulting in p.V600delinsYM. In vitro kinase assay and western blotting revealed that this mutation conferred high kinase activity of the BRAF protein, leading to constitutive activation of the mitogen-activated protein kinase (MAPK) signaling pathway. The degree of all the functional characteristics was comparable to that of BRAF^{V600E} [6, 7].

While BRAF inhibitors have shown significant activity against BRAF^{V600} mutant advanced melanoma in randomized phase III trials, it is not yet established that these agents will provide clinical benefit in patients with BRAF^{V600} mutant NSCLC.

Only few reports describe the efficacy of Vemurafenib in treating such patients, with complete responses reported within three to six weeks of administration, this subject is currently the focus of ongoing clinical trials [8-10].

Interim results from an international phase II trial, evaluating dabrafenib in V600E mutant NSCLC, were recently presented and revealed an overall response rate of 54% (7 partial responses of 13 patients evaluable for response, NCT01336634). However, the longest duration of response was 49 weeks at the time.

The discovery of BRAF mutations that activate the proliferative pathway of the MAPK is indeed a step forward in this regard since the high clinical value demonstrated in melanoma has made the pursuit of MAPK inhibitors one of the latest scientific inclinations.

Nonetheless, not all solid tumors share the same so-called "oncogene-addiction" resulting from BRAF mutations. This is best portrayed in colorectal adenocarcinoma (CRC) where BRAF^{V600E} mutations are now thought of as prognostic rather than predictive markers. In fact, BRAF-mutated CRC has a more aggressive clinical course than wild-type CRC with increased cancer-specific mortality rate [11].

However, patients with CRC harboring this mutation have a limited response to Vemurafenib [12]. In vitro studies suggest that unresponsiveness of CRC to inhibition by Vemurafenib is due to feedback activation of EGFR leading to activation of the protein RAS and in turn the dimerization of BRAF. Consequently, this induces Vemurafenib resistance because the drug cannot block RAF dimers [13].

Also comparable to CRC is a series of 1046 patients with NSCLC, where patients with BRAF^{V600E} mutation had a more aggressive tumor histology and shorter disease free survival and overall survival [14].

Our patient failed to demonstrate any clinical response following the administration of Vemurafenib while harboring a BRAF mutation that would confer high kinase activity mostly comparable to the BRAF^{V600E} mutation.

We believe our experience with this patient is quite valuable and many lessons ought to be considered.

First, it is a reminder for clinicians that we are still barely touching the tip of the iceberg despite all the recent progress in the intricate field of genomics. Such negative experiences should be shared since they hold as much value in the advancement of medicine as do positive experiences.

Moreover, easier access to molecular profiling and next generation sequencing could have detrimental ramifications, especially for patient care in underdeveloped countries. The growing number of publications, in medical journals as well as other sources, has been giving physi-

cians and non-physicians a glimpse of a foreseeable future where the most challenging tumors can be overcome with proper gene analysis. This somewhat distorted reality weighs a heavy burden for cancer patients in economically "challenged" countries that are lacking in terms proper healthcare provision. Patients in these countries tend to be more demanding when faced with a terminal illness; this is especially true in Middle Eastern populations. With the advent of exome sequencing at a relatively affordable price, this test appears as a necessity in the mentality of our patients and their family since failure to procure it would be perceived as a failure to provide the best possible care. The experience of our patient clearly portrays the heavy financial strain she has had to endure only to be faced with therapeutic failure.

We believe more effort should be made in order to keep both patients and physicians away from using off label therapeutics solely on the basis of mutational analysis. Standardized treatment regimens have proven their efficacy in cohort studies and should remain the norm for the time being, all other therapeutics that are not evidence based should remain in the context of clinical trials.

Disclosure of conflict of interest

None.

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