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Case report

BRAF V600E-mutated lung adenocarcinoma with metastases to the brain responding to treatment with vemurafenib

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ABSTRACT

Somatic *BRAF* mutations have been reported in 1–4% of non-small cell lung cancer (NSCLC), primarily in adenocarcinomas with the *BRAF* (V600E) mutation in about 50% of the cases. The role of BRAF mutation in NSCLC and the treatment for tumors with such mutations is still evolving. Our patient had metastatic NSCLC with metastases to her brain. Due to the *BRAF* (V600E) mutation in her tumor and her poor functional status, we offered her off-label treatment with vemurafenib, a BRAF inhibitor approved for use in metastatic melanoma. Our patient's visceral disease improved supporting vemurafenib's efficacy in the treatment of metastatic *BRAF*-mutated NSCLC. The regression of intracranial disease indicated vemurafenib was able to cross the blood–brain barrier and was efficacious in treating brain metastases in this patient with lung cancer.

1. Introduction

Targeted therapy in treatment of molecularly selected populations with non-small-cell lung cancer (NSCLC) is remarkably effective as measured by response rates, progression-free survival (PFS), and quality of life [1–3]. *EGFR*-mutant and *ALK*-rearranged lung adenocarcinoma patients show improved PFS with targeted therapies compared to cytotoxic chemotherapy. As new oncogene targets in NSCLC are identified, more novel targeted therapies are leading to patient benefit.

One of the newer driver mutations discovered in NSCLC is in the *BRAF* gene, which encodes for a serine/threonine kinase downstream from KRAS in the mitogen-activated protein kinase signaling cascade [4]. *BRAF* mutations recently have been shown to be important in melanoma, with a glutamine for a valine at residue 600 (V600E) being the most common variant [5]. More recently, lung adenocarcinomas were genotyped and found to have *BRAF* missense mutations in 3–4.9% of patient cases [6–8]. These mutations seem to be mutually exclusive of *KRAS* and *EGFR* mutations. Initial reports suggested that up to 50% of the *BRAF* mutations were the V600E alteration and were observed in patients who never-smoked [7]. This latter finding was not replicated in a subsequent study where increased prevalence of *BRAF* mutations in prior smokers, both V600E and non-V600E, was described [9]. In 883 tumors screened, 36 (4%) harbored *BRAF* mutations (V600E, 18; non-V600E, 18). Fourteen patients within the *BRAF* cohort were eligible for response assessment after platinum-based chemotherapy. V600E mutation patients ($n = 7$) had lower response rates and shorter median PFS (4.1 vs 8.9 months) than non-V600E mutation patients [9]. Median PFS of patients with advanced NSCLC treated with platinum-based chemotherapy was shorter (5.2 vs 6.7 months) for *BRAF*-mutant versus wild-type patients, respectively. This is consistent with a previous report of less favorable outcomes among patients with *BRAF* V600E mutations compared to *BRAF*-wild type [7]. Therefore, interim results of a phase II trial investigating use of the *BRAF* inhibitor, dabrafenib, for treatment of *BRAF* V600E-mutant metastatic NSCLC were timely. Treatment of patients with dabrafenib demonstrated early anti-tumor activity with overall response rates of 50% and a median progression free survival of 5.1 months; however, patients with brain metastases were excluded [10]. Herein we report off-label use of another BRAF inhibitor, vemurafenib, for a patient with *BRAF* V600E-mutant NSCLC with metastases to the brain.

2. Methods

TTF-1 immunohistochemistry was performed using the Bench-March System (Ventana Medical Systems, Inc., Tucson, AZ) using a TTF-1 clone (Dako North America, Inc., Carpenteria, CA; 8g7g3/1; lot#10078105 exp 05/2015) at a 1:100 dilution.

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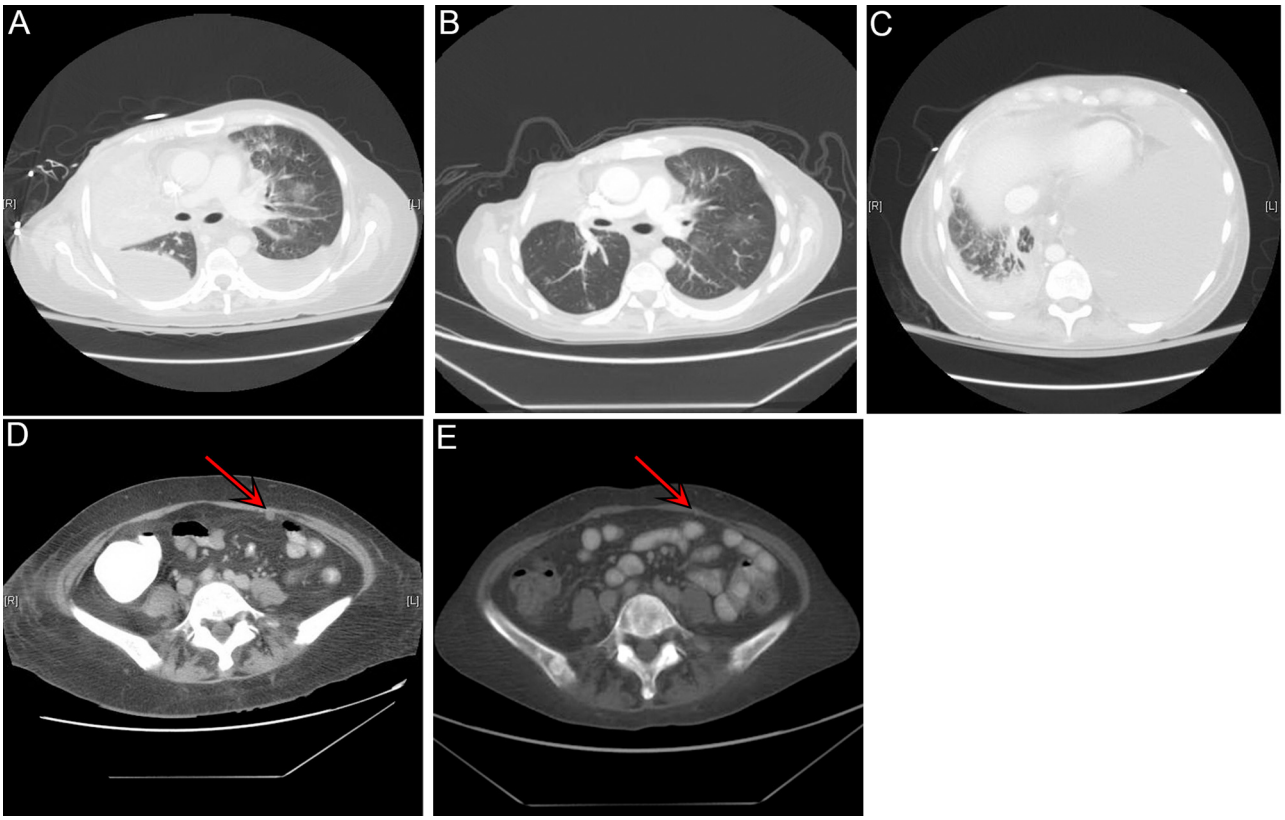

Fig. 1. CT images of the thorax and abdomen of the patient. (A) CT image of the chest at baseline. (B) CT image of the chest 4 weeks after starting vemurafenib. (C) CT image of the chest 5 months after presentation showing progression on vemurafenib. (D) CT of the abdomen prior to treatment. Omental nodule (red arrow). (E) CT of the abdomen 4 weeks after treatment. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Genomic profiling was performed in a CLIA-certified, CAP-accredited laboratory (Foundation Medicine, Inc., Cambridge, MA) using validated methods [11].

3. Case

A 51-year-old never-smoker woman with a history of locally advanced, inflammatory, invasive ductal carcinoma of right breast in 1999 presented to her oncologist 13 years later in 2013 complaining of shortness of breath and cough. Prior treatment for her inflammatory, ER/PR negative, HER2/neu positive breast cancer included preoperative chemotherapy and trastuzumab followed by a right mastectomy and then right chest wall and regional lymphatic irradiation.

At presentation in 2013, CT scan revealed a large right pleural effusion with thickening of the pleura concerning for pleural metastases. She had adenopathy in the left supraclavicular, mediastinal, and hilar areas, in addition to bilateral adrenal masses, a mass in the tail of the pancreas, pericardial effusion and omental nodules (Fig. 1A and D). Thoracentesis and a biopsy of a left supraclavicular lymph node demonstrated malignant cells consistent with metastatic adenocarcinoma. Immunohistochemical (IHC) pattern was suggestive of lung origin (TTF-1 positive, HER2/neu negative) (Fig. 2). Her original breast tissue was then evaluated and was negative for TTF-1.

The patient was admitted to the hospital with increasing shortness of breath and fatigue. She had a large right pleural effusion despite previous thoracentesis and a pericardial effusion, causing tamponade. She underwent a pericardial window pleural fluid drainage, right pleural catheter placement, and had a right upper lobe and pleural biopsy. Pathology was consistent with the supraclavicular node. She was diagnosed with metastatic carcinoma of the lung. Genomic evaluation using a targeted mutation panel by PCR showed a *BRAF* V600E mutation, which was confirmed on whole genome sequencing (Fig. 3).

As staging MRI of her brain showed multiple small supra- and infratentorial metastases, as well as osseous metastases present (Fig. 4A). CT of her abdomen and pelvis illustrated multiple peritoneal implants, ovarian masses, ascites, and a L4 vertebral body compression fracture. Given her poor functional status, and discovery of a possible driver mutation, a search for alternative therapies was undertaken. Results from a recent abstract had demonstrated an impressive response rate and PFS with the use of BRAF inhibition in BRAF-mutant NSCLC [10]. In addition, previous case reports suggested benefit with BRAF inhibitors in advanced NSCLC with a *BRAF* V600E mutation [12,13]. Based on these findings, we recommended treatment with the BRAF inhibitor vemurafenib at 960 mg twice daily.

One month later, the patient's symptoms improved. A CT showed improvement in the pleural right effusion. In addition, the para-aortic nodal group (4.6 cm decreased to 2.9 cm), pretracheal nodes as well as abdominal, pelvic, and osseous metastases showed significant responses (Fig. 1B and E). A repeat brain MRI showed a decrease in size of the intracranial metastases after 4 weeks of therapy (Fig. 4B).

The patient did relatively well over the next month despite a grade 2 maculopapular skin rash and grade 1 elevation in liver function tests. Repeat CT after 2 months (data not shown) of therapy showed further improvement in the patient's pleural-parenchymal opacifications, thoracic adenopathy, and osseous disease. Repeat MRI of the brain showed stable disease (data not shown).

Unfortunately, after 4 months of treatment, she developed respiratory distress. She was found to have worsening lung disease

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