**BRAF** V600Q-mutated lung adenocarcinoma with duodenal metastasis and extreme leukocytosis

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**Abstract**

Driver mutations in patients with non-small cell lung cancer (NSCLC) can lead to distinct behaviors and patterns of metastasis. Mutations in the proto-oncogene B-raf (**BRAF**) occur in approximately 3% of NSCLC cases. In the literature, reports of patients with lung adenocarcinomas metastasizing to the duodenum are rare, and most of the only 21 cases reported were from before the advent of next-generation sequencing. We present here a case involving a 57-year-old female who had a lytic lesion in her lesser trochanter. Biopsy showed metastatic adenocarcinoma of lung origin. Chest X-ray showed a large left upper lobe mass. Next-generation sequencing analysis confirmed the presence of **BRAF** V600Q mutation. The patient presented with persistent anemia and melena. Esophagogastroduodenoscopy confirmed the presence of duodenal metastasis. She also had suspected paraneoplastic leukemoid reaction. To our knowledge, this is only the second well-documented case of gastrointestinal metastasis from **BRAF**-mutated lung cancer.

**Key words:** **BRAF**; Lung adenocarcinoma; Duodenum; Metastasis; Gastrointestinal bleeding; Endoscopy; Leukocytosis
Our patient was a 57-year-old female with a known history of metastatic lung adenocarcinoma. Her history dated back to December 2015, when she developed left hip pain. It was initially treated conservatively and imaging examination was not performed. However, over the ensuing 4 mo, the pain worsened and became gnawing and constant. She was afebrile. Results from laboratory work-up revealed leukocytosis (19.3 × 10^9/L; reference range: 4.3-11 × 10^9/L) with 84% neutrophils, microcytic anemia (7.1 g/dL; reference range: 12-15.5 g/dL) with mean corpuscular volume (MCV) of 71 fL, and thrombocytosis (595 × 10^9/L; reference range: 150-450 × 10^9/L). At 4 mo prior, her hemoglobin had been 13.0 g/dL (reference range: 12-15.5 g/dL).

A computed tomography (CT) scan of the left hip was obtained, and showed marked irregularity of the lesser trochanter with cortical bone destruction. A soft tissue mass was also seen in the region of the cortex. A plain chest film revealed a large left lung mass. Iron studies revealed a ferritin level of 86 ng/mL, iron of <10 µg/dL (reference range: 50-160 µg/dL) and total-iron binding capacity of 353 µg/dL (reference range: 270-380 µg/dL). Other causes of anemia were ruled out. A peripheral smear showed microcytic hypochromic anemia and granulocytosis without left-shift.

The patient was transfused with a unit of packed red blood cells (PRBCs) and taken to the operating room. She underwent intralesional curettage, partial excision of the lesser trochanter, and open arthotomy of the left hip with extraction of the mass. Pathological examination of the extracted bone and soft-tissue mass revealed poorly differentiated metastatic adenocarcinoma cells. Immunohistochemical staining revealed strong reactivity for cytokeratin 7 (CK7) and thyroid transcription factor-1 (TTF-1) and negative reactivity for cytokeratin 20 (CK20) and GATA binding protein 3 (GATA3); these findings are most consistent with lung origin. CT scans revealed a large left upper lobe mass, measuring 8.5 cm × 6.7 cm × 10.7 cm, with extensive local invasion. In addition, there was a left adrenal mass indicative of metastatic disease.

Genetic testing of the tumor was carried out using Caris Molecular Intelligence® (Caris Life Sciences, Irving, TX, United States). The next-generation sequencing (NGS) analysis revealed exon 15 BRAF V600Q and exon 7 TP53 G215V mutations. No mutations or rearrangements were found in the genes for Kirsten ras viral oncogene (KRAS), neuroblastoma ras viral oncogene (NRAS), anaplastic lymphoma receptor tyrosine kinase (ALK), neuroblastoma ras viral oncogene (NRAS), anaplastic lymphoma receptor tyrosine kinase (ALK), tyrosine-protein kinase Met (cMET), EGFR, ROS1, retinoblastoma-1 (RB1), phosphatidylinositol-4,5- bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), or ret proto-oncogene (RET).

The patient received palliative radiotherapy to the left femur. Her anemia was considered likely multifactorial, given the active malignancy with possible iron deficiency. Ferrous sulfate supplementation was initiated (oral; 325 mg regular-release twice daily), but only minimal improvement in her anemia was observed. Of note, her leucocyte count remained elevated after the surgery (18.9-56.4 × 10^9/L). She had no signs of...
infection or inflammation.

After the radiotherapy, two cycles of carboplatin and pemetrexed were administered. However, shortly after the second cycle, the patient presented to the emergency room with increasing shortness of breath and weakness. She also reported intermittent melanotic stool for the past few days. Physical exam revealed pallor and almost no air entry into the left part of the chest on auscultation. She was afebrile. Laboratory investigations showed a leucocyte count of $80.2 \times 10^9/L$ with 92% neutrophils, 6% monocytes and 2% lymphocytes, hemoglobin of 6.0 g/dL, and platelet count of $519 \times 10^9/L$. Guaiac fecal occult blood test was positive. CT scan showed extensive growth of the upper lobe mass (to 14.5 cm x 10.0 cm x 17.4 cm) with progressive mediastinal invasion (Figure 1).

The patient was admitted to the hospital and transfused with 1 U of PRBCs. Esophagogastroduodenoscopy was performed, and an ulcerated bleeding 1-cm mass with malignant appearance was found in the second part of the duodenum (Figure 2). The scope could not traverse the lesion, and the exam could not be finished. Cold forceps biopsies were taken. On pathological exam, poorly differentiated adenocarcinoma was determined. The morphological and immunohistochemical characteristics of the tumor were similar to the findings on the original bone biopsy, being consistent with lung origin.

The patient’s leukocytosis worsened (up to $102 \times 10^9/L$, with 92% neutrophils, 3% monocytes, 2% myelocytes, 1% metamyelocytes, 1% promyelocytes and 1% lymphocytes). She did not have fever or other signs of infection. She did not receive any granulocyte-stimulating agent with her chemotherapy and did not receive steroids. A peripheral smear showed absolute neutrophilia with coarse toxic granulation and Döhle bodies in numerous neutrophils and with occasional metamyelocytes and myelocytes. In addition, rare nucleated red blood cells were observed. Peripheral flow cytometry did not show any increase in blast count. Mutational analysis showed no mutation in the genes for Janus kinase-2 (JAK-2), calreticulin (CALR) and colony-stimulating factor 3 receptor (CSF3R). In addition, reverse-transcriptase polymerase chain reaction assay of peripheral blood gave negative results for BCR-ABL b2a2, b3a2, and e1a2 fusion gene transcripts. This finding lessened the likelihood of chronic myeloid leukemia as well as of chronic myeloproliferative disorders. Given the patient’s very poor prognosis, bone marrow examination was not performed.

Considering the patient’s rapid course of progression and development of resistance to frontline chemotherapy, she was started on the off-label combination of dabrafenib with trametinib, which has Federal Drug Administration approval for use in BRAF-mutated melanoma. Unfortunately, her clinical condition deteriorated quickly and she died around 2 wk after her presentation.
DISCUSSION

The BRAF gene on chromosome 7 (7q34) is a proto-oncogene that encodes the serine/threonine specific protein kinase family member BRAF\(^{[9]}\). The BRAF protein participates in the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway, which is also known as the Ras-Raf-mitogen-activated protein kinase kinase (MEK)-ERK pathway\(^{[1]}\). It is a chain of proteins that functions in the signaling from cell surface to the nucleus\(^{[1]}\). Activation of this pathway leads to synthesis of transcription factors that are important in cell cycle regulation\(^{[7]}\). Mutations in MAPK/ERK can lead to uncontrolled growth and neoplastic transformation. BRAF mutations were first described in 2002 and occur in varying frequencies in melanoma, colorectal carcinomas, and lung, thyroid and other types of malignancies\(^{[9]}\).

BRAF is mutated in approximately 3% of patients with NSCLC (mainly of adenocarcinoma type)\(^{[9]}\). The most commonly observed mutation in BRAF is the valine (V) to glutamic acid (E) substitution at codon 600 (BRAF V600E) on exon 15\(^{[10]}\), BRAF V600E accounts for about 50% of the BRAF mutations in NSCLC cases\(^{[11]}\). A large meta-analysis found that the BRAF V600E mutation was more frequent in women and was closely related a history of never-smoking\(^{[9]}\). In addition, one study showed that V600E-mutated tumors had an aggressive histotype and were significantly associated with shorter disease-free and overall survival rates\(^{[12]}\). Two other studies showed that V600E-mutated tumors responded less favorably to platinum-based chemotherapy, although the finding did not reach statistical significance\(^{[13,14]}\). In contrast, other studies have shown that overall survival was not statistically different between patients with wild-type BRAF and those with V600E or non-V600E BRAF mutations\(^{[10,11,15]}\).

Our patient had metastasis to the duodenum. The immunohistochemical pattern of her bone and duodenal biopsies was suggestive of adenocarcinoma originating in the lung. In general, positive staining for TTF-1 and CK7, in addition to negative CK20 staining (i.e., TTF1+/CK7⁻/CK20⁺ pattern) strongly supports a lung origin, as opposed to a gastrointestinal origin\(^{[16]}\). Metastases to the small bowel from lung cancer are very rare and usually asymptomatic\(^{[4]}\). According to a literature review by Hillenbrand et al\(^{[1]}\) published in 2005, clinically-manifested small bowel metastasis was documented in 58 reports between 1961 and 2003. The most common symptoms were perforation and/or obstruction, or less commonly, bleeding.

Duodenal metastasis from lung cancer is exceedingly rare. AlSaeed et al\(^{[3]}\) reported a case of duodenal metastasis from lung adenocarcinoma and cited another 11 previous reports. In addition, we found 9 more cases of lung cancer with duodenal metastasis\(^{[17-22]}\). Out of the 21 total cases reported, 9 showed adenocarcinoma histology, 7 showed squamous cell histology, 2 showed large cell histology, 2 showed small cell histology, and 1 was deemed unspecified NSCLC. Symptoms of gastrointestinal bleeding and/or iron deficiency occurred in 13 cases. Other reported clinical features include obstructive jaundice, abdominal pain, obstruction, and perforation. None of the reported cases had accompanying molecular analyses data for driver mutations.

We have previously reported a case of BRAF V600E-mutated lung adenocarcinoma, which had an aggressive clinical course and gastric metastases\(^{[24]}\). Herein, we present another case with a similar aggressive course and duodenal metastasis. Previous reports and studies have not indicated the association between certain genetic mutations in lung cancer and the predilection to gastrointestinal metastasis. In addition, gastric or intestinal metastases are rare and difficult to diagnose on imaging, and most of the reported cases of gastrointestinal metastases from lung cancer occurred before the discovery of driver mutations. Therefore, it cannot be proven that the BRAF mutation contributed to the gastric or duodenal metastasis in the previously reported cases.

We suggest that in cases of lung cancer with BRAF V600E mutations, an aggressive behavior must be expected. In addition, gastrointestinal tract involvement must be kept in mind. Clinical research on a larger scale (rather than relying on the rare case reports) will be imperative to understand the incidence of gastrointestinal involvement. In addition to mutated BRAF, our patient had a missense mutation in codon 245 of exon 7 of the TP53 gene (G245V). This mutation occurred in the DNA-binding site of the protein and was previously reported in lung cancer\(^{[25]}\). A previous, large meta-analysis found that TP53 mutations conferred worse clinical outcomes in patients with NSCLC, especially in those with adenocarcinoma histology\(^{[26]}\). It is possible that the TP53 mutation in our patient contributed to the aggressive clinical course and resistance to chemotherapy.

Another interesting feature of our case was the extreme neutrophilia. Infections and myeloproliferative disorders were unlikely in the absence of fever or signs of infection, JAK-2 mutations, or BCR-ABL rearrangements. Bone marrow infiltration from adenocarcinoma cells was a possibility, given the presence of rare nucleated red blood cells in the peripheral smear. Unfortunately, the patient’s bone marrow was not examined. It is also possible that her poor outcome was related to a paraneoplastic leukemoid reaction. Interestingly, neutrophilic leukemoid reaction was reported in a patient with BRAF V600E-mutated metastatic melanoma\(^{[27]}\). In another report, a case of squamous cell carcinoma with peritoneal carcinomatosis and an eosinophilic leukemoid reaction showed coexistence of the BRAF V600E and oncogenic KRAS G12A mutations\(^{[28]}\). Up-regulation of granulocyte colony-stimulating factor (G-CSF) through RAS/RAF/MEK pathway activation can lead to a paraneoplastic leukemoid reaction\(^{[29]}\).

Finally, dabrafenib and trametinib are small molecule
inhibitors of BRAF and MEK1/MEK2, respectively. Their oral administration combination is approved for treatment of BRAF V600E-mutated melanoma and is currently being investigated for lung cancer harboring the mutation. In that trial, the overall response rate was 63%, with the median duration of response being 9 mo. We started our patient on dabrafenib and trametinib. Unfortunately, she died of her disease before any response was observed.

In conclusion, certain molecular mutations in NSCLC might lead to unique clinical behaviors. We have described a case of lung adenocarcinoma which had an atypical and aggressive clinical course, with duodenal metastasis and extreme leukocytosis. We have performed molecular analysis using NGS, which showed the mutations of exon 15 BRAF V600Q and exon 7 TP53 G245V. To the best of our knowledge, this is only the second reported case of well-documented BRAF-mutated lung adenocarcinoma with metastases to the gastrointestinal tract. Indeed, the continued use of modern molecular methods, such as NGS, will allow us to explore possible correlations between certain mutations and clinical behaviors.

**COMMENTS**

**Case characteristics**
A 57-year-old female with metastatic lung adenocarcinoma mutation in the proto-oncogene B-raf (BRAF) gene with presentation of fatigue, increasing shortness of breath and melena.

**Clinical diagnosis**
Pallor and almost no air entry into the left part of the chest on auscultation.

**Differential diagnosis**
Peptic ulcer disease, esophagitis, gastritis, duodenitis, vascular lesions or tumors.

**Laboratory diagnosis**
Anemia, extreme leukocytosis, and positive hemoccult stool test.

**Imaging diagnosis**
Computed tomography chest scan showing rapid progression of the cancer. Imaging diagnosis: Anemia, extreme leukocytosis, and positive hemoccult stool test.

**Pathological diagnosis**
The morphological and immunohistochemical characteristics of the tumor were similar to the findings on the original biopsy, being consistent with lung origin.

**Treatment**
Dabrafenib and trametinib were started, but the patient died before any response was observed.

**Related reports**
This is only the second well-documented case of gastrointestinal metastasis from BRAF-mutated lung cancer.

**Term explanation**
The BRAF gene is a proto-oncogene that encodes the serine/threonine specific protein kinase family member BRAF. The BRAF protein participates in the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway.

**Experiences and lessons**
BRAF-mutated lung adenocarcinoma can be aggressive. Further studies are needed to explore possible correlations between BRAF mutations and clinical behaviors. Furthermore, treatment with dabrafenib and trametinib has promising results.

**Peer-review**
The object is interesting and the manuscript clearly reported. This is the second well-documented case of gastrointestinal metastasis from BRAF-mutated lung cancer.

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