CASE REPORT

BRAF-Mutant Pulmonary Langerhans Cell Histiocytosis Mimicking Recurrence of Early-Stage *KRAS*-Mutant Lung Adenocarcinoma

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Surveillance imaging after the resection of early-stage lung cancer is the primary method for identifying recurrence; however, new pulmonary nodules on the imaging may result from multiple alternative causes. We describe a patient with early-stage lung adenocarcinoma, treated with platinum-doublet chemotherapy and programmed cell death protein 1 inhibitor followed by surgical resection, who developed bilateral pulmonary nodules concerning for progression.

Case Report

A 45-year-old woman with chronic obstructive pulmonary disease and currently use tobacco (>30 pack-years) presented with right-sided chest pain, hemoptysis, and night sweats. Initial computed tomography (CT) imaging results revealed a 2.1-cm spiculated right upper lobe lesion (Fig. 1*A*) and right hilar and right paratracheal adenopathy. The results of a 4R lymph node biopsy revealed lung adenocarcinoma (Fig. 2*A*), consistent with stage IIIB disease and a programmed death-ligand 1 tumor proportion score of 70% (Fig. 2*B*). She received an investigational neoadjuvant regimen of platinum, pemetrexed, and a programmed cell death protein-1 inhibitor, followed by right upper and lower lobe wedge resections with lymph node dissection. Right upper lobe histopathology revealed a fibrotic nodule with chronic inflammation in a 1.3-cm tumor bed, with no residual viable tumor in the primary tumor and eight hilar and mediastinal lymph nodes, consistent with complete histopathologic response (Fig. 2*C*). A separate lesion was found in the right lower lobe (Fig. 2*D*), present in a background of smoking-related changes, including desquamative interstitial pneumonia-type airspace filling and nodular peribronchiolar scars; results of Langerin and CD1a stains revealed scattered Langerhans cells. This lesion had a programmed death-ligand 1 tumor proportion score of 0% and *KRAS* G12D mutation, without other oncogenic alterations (Fig. 3*A*).

Imaging 1 month after the surgery was unremarkable. The patient developed pleuritic chest pain 2 months after the surgery, and a chest CT result revealed scattered, small nodules bilaterally, predominantly in the upper lobes of the lungs, with unchanged lymphadenopathy (Fig. 1*B*). The chest CT result approximately 3 months after the surgery revealed new, increasing

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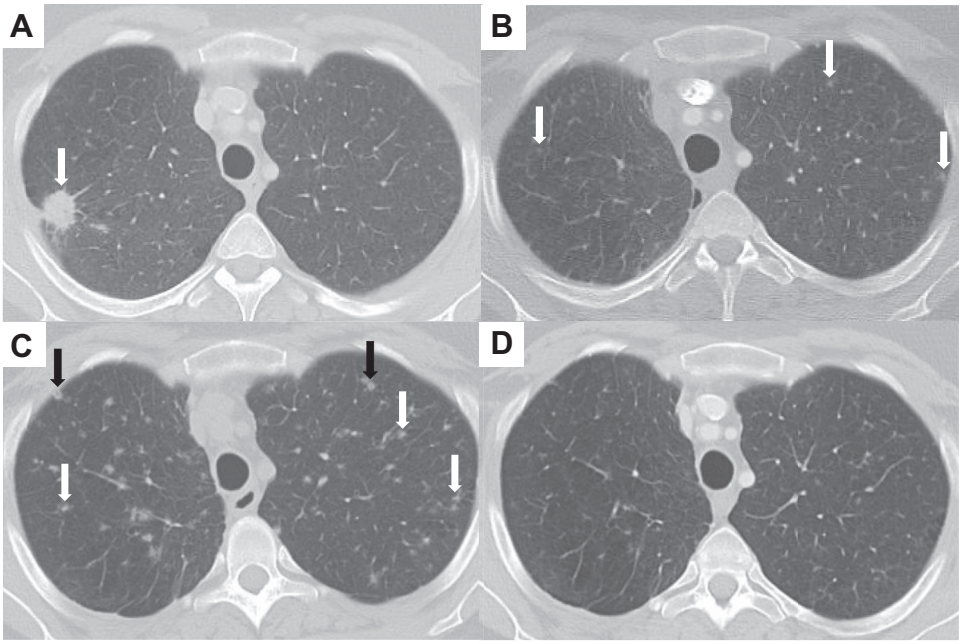

Figure 1. CT scan of the chest. (*A*) The patient's right upper lobe lesion (arrow) was noted on initial presentation. (*B*) Two months after wedge resection of the patient's primary tumor, the imaging result revealed the development of bilateral pulmonary nodules (arrows), predominantly in the upper lobes of the lungs. (*C*) A repeat CT scan 3 months after the surgery revealed increased size and density of these irregular nodules (arrows), which are somewhat centrilobular in distribution; some nodules had cavitation (black arrows). (*D*) Imaging 4 months after the diagnosis of LCH revealed a decrease in size and density of these nodules. CT, computed tomography; LCH, Langerhans cell histiocytosis.

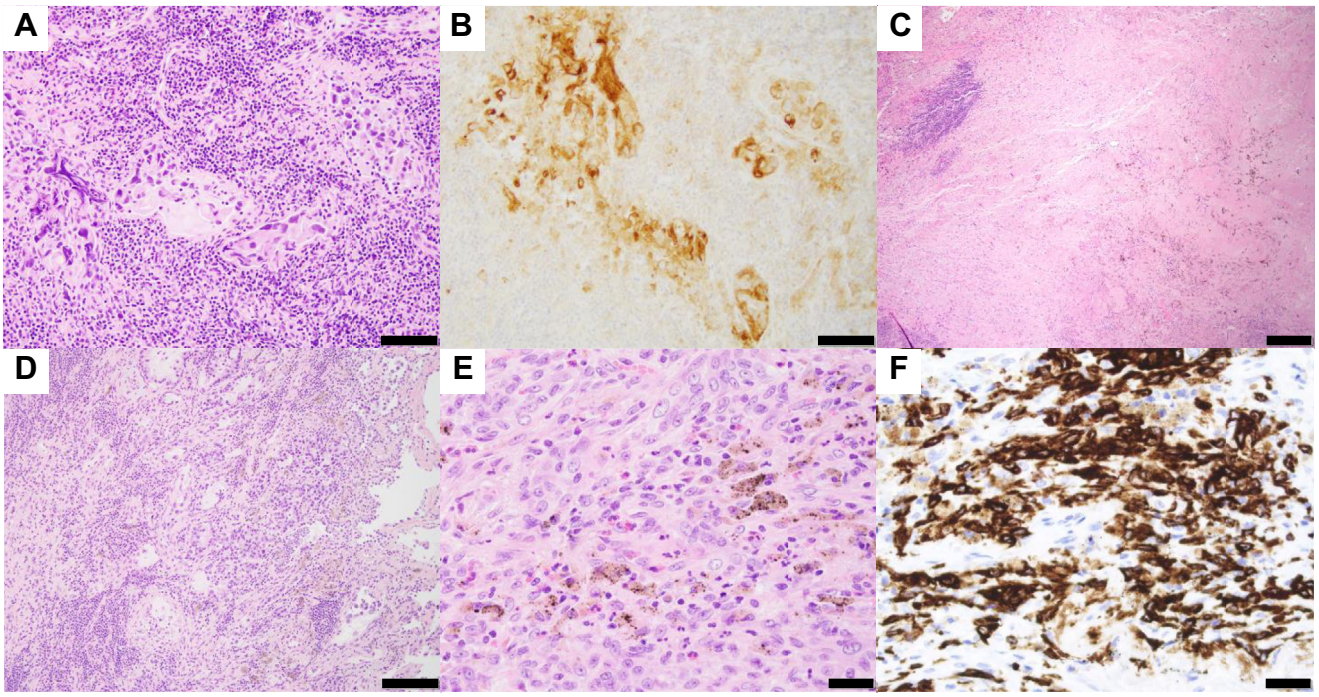

Figure 2. Histologic findings. (*A*) The result of the patient's initial 4R lymph node biopsy (H&E) revealed lung adenocarcinoma, (*B*) with PD-L1 immunohistochemistry revealing a TPS of 70%. (*C*) After chemoimmunotherapy and surgery, the right upper lobe tumor bed (H&E) had complete pathologic response, (*D*) whereas the right lower lobe lesion (H&E) was found to contain adenocarcinoma. (*E*) A sample of the left upper lobe tissue obtained after the development of bilateral pulmonary nodules (H&E) was found to have nodules of histiocytes and eosinophils in a fibrous background, consistent with pulmonary LCH, confirmed by immunohistochemical staining for (*F*) Langerin. Scale bars are as follows: (*A*) 50 μm, (*B*) 50 μm, (*C*) 200 μm, (*D*) 100 μm, (*E*) 20 μm, and (*F*) 20 μm. H&E, hematoxylin and eosin; LCH, Langerhans cell histiocytosis; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

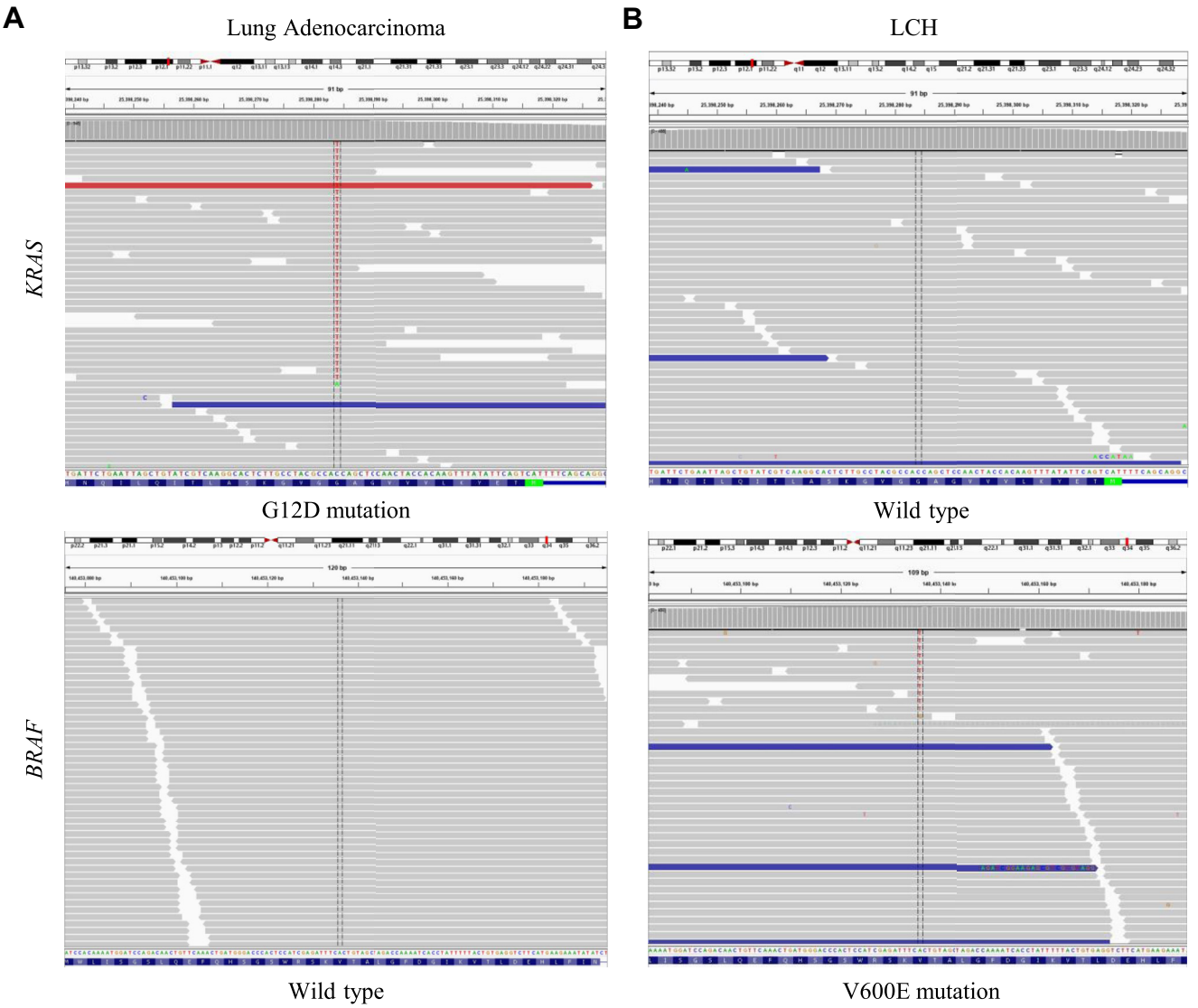

Figure 3. Genomic sequencing. (*A*) Tissue from the patient's right upper lobectomy containing the primary tumor revealed a *KRAS* c.35G>A (p.G12D) mutation (top panel) and *BRAF* wild type (bottom panel). (*B*) Sequencing of tissue from the patient's wedge resection containing the pulmonary LCH identified a *BRAF* c.1799T>A (p.V600E) mutation (bottom panel) with no *KRAS* mutation (top panel). LCH, Langerhans cell histiocytosis.

nodules, and the patient underwent diagnostic left upper lobe wedge resection. Histopathologic examination revealed Langerhans cell histiocytosis (Fig. 2*E*), positive for CD1a, Langerin (Fig. 2*F*), and S100, without evidence of recurrence. Genomic sequencing identified a *BRAF* V600E mutation and no *KRAS* mutation (Fig. 3*B*). The imaging 1 month after the patient's left upper lobe resection revealed irregular nodules (Fig. 1*C*), with subsequent scans after tobacco reduction revealing reduced nodule size and density (Fig. 1*D*).

Discussion

There are many radiographic mimics of lung cancer, including lymphoproliferative disorders, infectious or inflammatory processes, vascular conditions, and second malignancy.[1-3] Given previous treatment with an immune checkpoint inhibitor, an immune-related pneumonitis must be considered.[4] Although pulmonary Langerhans cell histiocytosis is rarely diagnosed in the setting of lung cancer, reports in association with primary lung cancers exist.[5] It is challenging to exclude lung cancer recurrence on the basis of imaging and clinical findings alone, and, in our patient, coexisting lymphadenopathy increased the concern for malignant progression.[3] Although recurrent malignancy must be considered with new or progressing imaging findings, histopathologic analysis is critical in distinguishing cancer recurrence from alternative diagnoses.

Acknowledgments

The patient provided a written consent to the Institutional Review Board–approved protocols at the Dana-Farber/Harvard Cancer Center, allowing for chart review and genomic sequencing on the tissue and plasma samples (Dana-Farber/Harvard Cancer Center protocol #02-180).

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