Lung Adenocarcinoma in Primary Ciliary Dyskinesia: A Case Report of Metastatic Disease and Successful Multimodal Treatment

Vishnu Kommineni, MBBS, MD, MBA; Rathnamitreyee Vegunta, MBBS, MD; Venkata Rokkam, MD; Gurusaravanan Kutti Sridharan, MD

ABSTRACT

Introduction: Primary ciliary dyskinesia (PCD) is a rare genetic disorder characterized by impaired mucociliary clearance. To our knowledge, no cases of lung adenocarcinoma in patients with PCD have been previously reported.

Case Presentation: A 43-year-old White man with PCD presented with persistent cough and dysphonia. Chest imaging revealed a 4-cm mass in the left upper lobe, and positron emission tomography/computed tomography (PET/CT) demonstrated increased uptake in the mass, hilar lymph nodes, and sternum, suggesting metastatic disease. Biopsy of the lung mass confirmed adenocarcinoma, and magnetic resonance imaging of the brain identified a metastatic lesion. He was treated initially with pembrolizumab and stereotactic radiation therapy for a brain metastasis and had a mixed response. Consequently, chemotherapy with carboplatin and pemetrexed was added, resulting in complete response, with no fluorodeoxyglucose-avid lesions on follow-up PET imaging.

Discussion: With only 8 reported cases of lung cancer in patients with PCD, this is, to our knowledge, the first report of lung adenocarcinoma in a patient with PCD successfully treated with chemoimmunotherapy.

Conclusions: Although rare, clinicians should consider lung cancer in patients with PCD who present with persistent symptoms refractory to standard treatment.

INTRODUCTION

Primary ciliary dyskinesia (PCD) is a rare inherited condition characterized by impaired mucociliary clearance due to genetic mutations affecting motile cilia. It primarily follows an autosomal recessive inheritance pattern, although other patterns, including autosomal dominant and X-linked inheritance, also occur. PCD affects approximately 1 in 10 000 to 20 000 live births.[1] Primary lung cancer among patients with PCD is rare.

CASE PRESENTATION

A 43-year-old White man presented with cough, chest pain, headache, and hoarseness that had persisted for several months. He was a never-smoker but chewed tobacco for 10 years before quitting 2 years prior to presentation. He had a history of recurrent bronchiectasis since childhood. Testing for cystic fibrosis and alpha-1-antitrypsin deficiency was negative. Electron microscopy of cilia showed partial absence of the inner dynein arms, leading to a diagnosis of PCD. Pulmonary function testing revealed severe chronic obstructive pulmonary disease (COPD).

A chest x-ray identified a focal opacity in the left upper lobe. Subsequent computed tomography (CT) of the chest revealed severe bilateral bronchiectasis and a 4-cm mass in the left upper lobe. Positron emission tomography/computed tomography (PET/CT) scan showed left hilar lymphadenopathy, sternal metastasis, and the 4-cm mass in the left upper lobe (Figures 1A and 2). A CT-guided biopsy of the lung mass confirmed lung adenocarcinoma. Staging workup with magnetic resonance imaging (MRI) of the brain revealed a 7-mm lesion in the left parietal lobe, leading to a diagnosis of stage IV (T2N1M1b) lung adenocarcinoma (Figure 3). Mutation testing was negative for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), and other mutations. Programmed death ligand 1 (PD-L1) testing revealed a tumor proportion score of 95%.

Given the treatment options for oligometastatic non-small cell

• • •

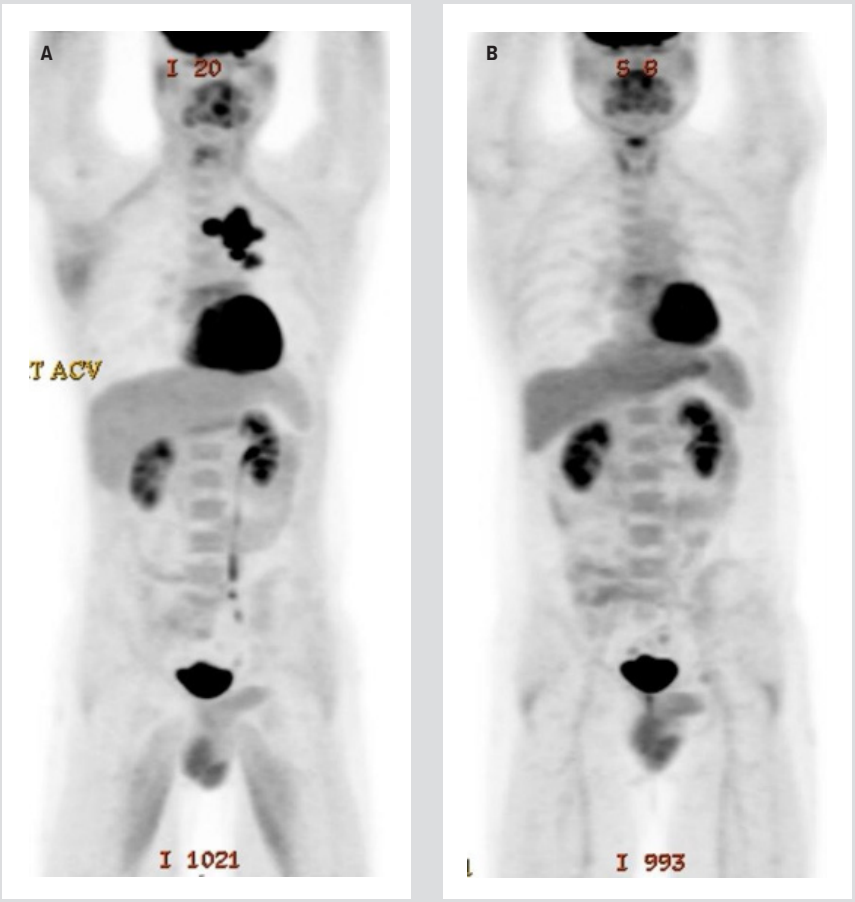
Author affiliations: Hospital Internal Medicine, Mayo Clinic Health System, Eau Claire, Wisconsin (Kommineni); Hematology and Oncology, Westchester Medical Center, Valhalla, New York (Vegunta); Internal Medicine, University of Arizona College of Medicine, Tucson, Arizona (Rokkam, Sridharan).

Corresponding author: Vishnu Kommineni, MBBS, MD, MBA, 1221 Whipple St, Eau Claire, WI 54703; email Kommineni.Vishnuteja@Mayo.edu; ORCID ID 0009-0005-6776-3592

lung cancer, including chemoradiation therapy, chemoimmunotherapy, or immunotherapy alone, the decision was made to treat the patient with immunotherapy alone because of his severe COPD, bronchiectasis, PCD, and high PD-L1 expression. He was started on intravenous (IV) pembrolizumab 200 mg every 3 weeks. After the first cycle of pembrolizumab, his hoarseness improved. He received stereotactic radiation therapy for the brain metastasis. During immunotherapy, he developed hypothyroidism and was started on thyroid hormone replacement therapy.

After 8 cycles of pembrolizumab, a repeat chest CT scan showed a mixed response to therapy, with near resolution of the left lung lesions but new nodules in the right middle lobe (Figure 4). An MRI of the brain showed no evidence of recurrent disease. As the patient had no clinical symptoms, laboratory abnormalities, or imaging findings suggestive of infection or inflammation (eg, ground glass opacities, organizing pneumonia), the decision was made to forego biopsy of the new right middle lobe lesions and add chemotherapy to ongoing immunotherapy. He received carboplatin, pemetrexed, and pembrolizumab every 3 weeks for 4 cycles and tolerated the therapy well, with no infectious complications. A follow-up chest CT after these 4 cycles showed an excellent response to therapy, with no new metastasis.

Figure 1. Positron Emission Tomography Scan Coronal View



A. Initial PET scan with increased uptake in the left upper chest and sternum.
B. Follow-up PET scan after completion of chemoimmunotherapy. Notice resolution of left upper chest lesions seen in Figure 1A.

He subsequently received maintenance treatment with pembrolizumab and pemetrexed for 4 cycles. However, he developed severe psoriasis secondary to immunotherapy, and further treatment was withheld. A follow-up PET/CT scan demonstrated a complete response to therapy, with no fluorodeoxyglucose-avid lesions (Figure 1B). Sixty-six months after initial presentation, he remained under surveillance with no evidence of recurrence.

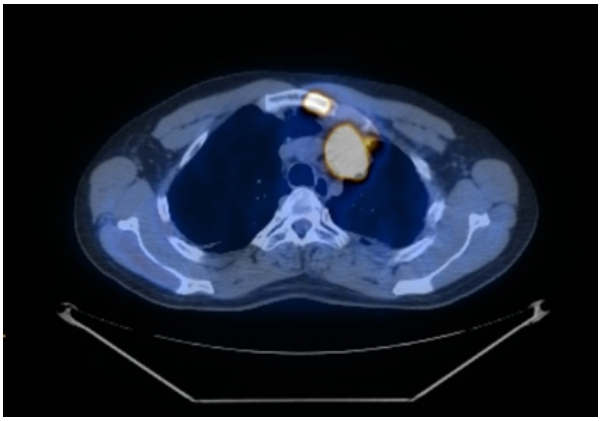
DISCUSSION

PCD is part of a growing group of genetic disorders known as ciliopathies. Mutations in genes encoding the axonemal structure and the cytoplasmic and regulatory proteins involved in the structure and function of motile cilia lead to PCD. Due to the large number of proteins involved in ciliary function and assembly, PCD exhibits substantial genetic heterogeneity. Patients typically present early in life and with a wide range of clinical manifestations caused by impaired mucociliary clearance. These manifestations include neonatal respiratory distress, persistent sinonasal disease, middle ear disease, hearing loss, chronic daily cough, bronchiectasis, and laterality defects. The severity of these symptoms varies according to the specific genotype involved.[1]

Diagnosing PCD is challenging because no single test can definitively confirm or exclude the disease. Historically, transmission electron microscopy (TEM) to assess axonemal ultrastructure has been considered the gold standard; however, limitations of electron microscopy have become apparent with advances in genetic tools.[1] Various subtypes of PCD have been identified based on the ultrastructural and functional ciliary defects. Diagnostic tools include nasal nitric oxide measurement, high-speed video microscopy, TEM, and genetic studies.[1,2] One notable subtype of PCD with situs inversus, chronic sinusitis, and bronchiectasis is Kartagener syndrome.

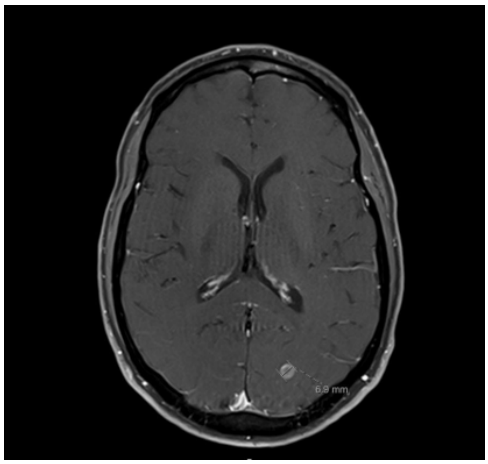
The relationship between PCD and lung cancer is not fully understood. Only 8 cases of lung cancer have been reported in patients with ciliary dyskinesia or Kartagener syndrome. Most of these patients were male (7 of 8) and older than 50 years (6 of

Figure 2. Initial PET/CT in Transverse Plane Showing Increased Uptake in the 4-cm Left Upper Lobe Mass With Left Hilar Lymph Nodes and Sternal Metastasis



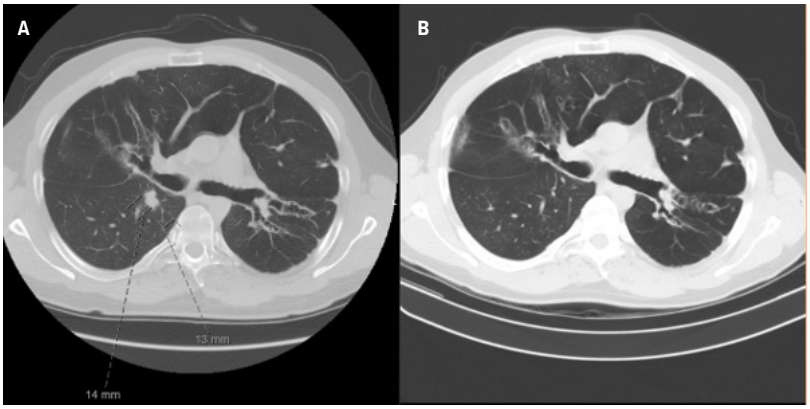
Abbreviation: PET/CT, positron emission tomography/computed tomography.

Figure 3. Magnetic Resonance Imaging of the Brain Showing a 7-mm Metastatic Lesion in the Left Parietal Lobe



8). No predilection for tumor laterality has been observed.[3,4] Squamous cell carcinoma was the most frequently reported histologic subtype (4 of 8 cases). Because most patients with PCD who developed lung cancer had a smoking history (5 of 6 cases), chronic inflammation related to smoking and emphysema has been proposed as a risk factor for squamous cell carcinoma.[5] PCD is associated with recurrent respiratory tract infections and bronchiectasis, both of which contribute to chronic pulmonary inflammation. Chung et al reported an increased risk of lung cancer in patients with bronchiectasis.[6] In a unique case, mucoepidermoid carcinoma was reported in a 39-year-old female never-smoker with Kartagener syndrome, with some evidence suggesting a possible role for congenital lung malformation.[4] Further research is needed to understand the pathophysiology underlying PCD-associated lung cancer across histologic subtypes and its association with never-smokers.

Figure 4. Computed Tomography of the Thorax



A. CT image after 8 cycles of pembrolizumab with new lung nodules in the right middle lobe.
B. CT image of the same section of thorax at the time of diagnosis.

Treatment options for oligometastatic non-small cell lung cancer include chemotherapy with immunotherapy, immunotherapy alone, or chemoradiation therapy. The KEYNOTE-024 trial demonstrated improved progression-free survival and overall survival among patients with PD-L1 expression greater than 50% who received pembrolizumab compared with platinum-doublet chemotherapy.[7] According to National Comprehensive Cancer Network guidelines, the addition of pembrolizumab to platinum-doublet chemotherapy is the preferred first-line treatment for non-small cell lung cancer with PD-L1 expression >1%, no contraindications to PD-1 or PD-L1 inhibitors, and no EGFR exon 19 deletion, EGFR L858R mutation, or ALK, RET, or ROS1 rearrangement.[8] However, treatment should be individualized based on each patient's comorbidities. To our knowledge, this is the first reported case of metastatic lung adenocarcinoma in a patient with PCD successfully treated with a combination of chemotherapy and immunotherapy.

CONCLUSIONS

The possibility of lung malignancy should be considered in patients with PCD who present with persistent respiratory symptoms refractory to standard treatment. Combination chemotherapy and immunotherapy can be administered safely to patients with lung adenocarcinoma and PCD.

Financial disclosures: None declared.

Funding/support: None declared.

REFERENCES

1. Horani A, Ferkol TW. Understanding primary ciliary dyskinesia and other ciliopathies. *J Pediatr.* 2020;230:15-22.e1. doi:10.1016/j.jpeds.2020.11.040

2. Frommer A, Hjeij R, Loges NT, et al. Immunofluorescence analysis and diagnosis of primary ciliary dyskinesia with radial spoke defects. *Am J Respir Cell Mol Biol.* 2015;53(4):563-573. doi:10.1165/rcmb.2014-0483OC

3. Inoue Y, Suga A, Sekido Y, Yamada S, Iwazaki M. A case of surgically resected lung cancer in a patient with Kartagener's syndrome. *Tokai J Exp Clin Med*. 2011;36(2):21-4.

4. Nagai Y, Koyama N, Iwai Y, et al. Pulmonary mucoepidermoid carcinoma arising in a patient with Kartagener syndrome. *BMC Pulm Med*. 2020;20(1):93. doi:10.1186/s12890-020-1133-y

5. Papi A, Casoni G, Caramori G, et al. COPD increases the risk of squamous histological subtype in smokers who develop non-small cell lung carcinoma. *Thorax*. 2004;59(8):679-681. doi:10.1136/thx.2003.018291

6. Chung WS, Lin CL, Hsu WH, Kao CH. Increased risk of lung cancer among patients with bronchiectasis: a nationwide cohort study. *QJM*. 2016;109(1):17-25. doi:10.1093/qjmed/hcu237

7. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med.* 2016;375(19):1823-1833. doi:10.1056/NEJMoa1606774

8. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med.* 2018;378(22):2078-2092. doi:10.1056/NEJMoa1801005

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 2379-3961) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

Visit www.wmjonline.org to learn more.