

Pulmonary Arterial Hypertension in a Patient With Metastatic Lung Cancer on Pembrolizumab: Whom to Blame?

Lakshmi Manogna Chintalacheruvu^{a, d}, Vamsi Krishna Chilluru^b,
Narendra Babu Gutta^c

Abstract

Immune checkpoint inhibitors (ICIs) play a major role in current cancer treatments. They are associated with immune-mediated side effects due to immune dysregulation. ICI-mediated complications are more commonly known to affect thyroid gland, gastrointestinal system, skin, etc. Pulmonary arterial hypertension (PAH) due to ICIs is not very well described in the literature. Here, we report a case of severe PAH diagnosed in a patient with metastatic lung cancer on long-term pembrolizumab and literature review.

Keywords: Pulmonary hypertension; Immune checkpoint inhibitors; Pembrolizumab; Lung cancer; Pulmonary artery diameter; Aorta diameter

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment since its approval [1]. They predominantly target immunoregulatory molecules such as programmed cell death-1 (PD-1), program cell death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) [1]. Pembrolizumab is an ICI that targets the PD-1 pathway, thereby activating T cells to attack cancer cells [2]. This can cause immune dysregulation with increased inflammation and increased tissue damage, which can happen in any organ [1]. Common side effects associated with pembrolizumab include fatigue (19.4%), pruritus (10.7%), poor appetite (10.5%), and rash (9.7%) [3]. Pulmonary side effects such as pneumonitis (3.6%) and cough (2.4%) are rare and pulmonary arterial hypertension (PAH) is

not highly reported in clinical trials [3]. Here, we report a case of severe PAH diagnosed in a patient with metastatic lung cancer on ICI pembrolizumab.

Case Report

A 71-year-old male with a past medical history of tobacco use, who quit more than 24 years ago with no other significant comorbidities, was referred to the clinic for newly diagnosed lung cancer. He initially noticed a lump in the right axilla, progressively increasing in size over the period of 2 months. Axillary ultrasound showed a 3.7 cm enlarged lymph node (LN) in the right axilla with effacement and hypervascularity. LN biopsy showed carcinoma with cytokeratin 7 (CK-7) and thyroid transcription factor-1 (TTF-1) positivity. P40 is focally positive, indicating findings consistent with lung adenocarcinoma, with a possibility of squamous component. Positron emission tomography (PET) scan showed multiple F-fluorodeoxyglucose (FDG) avid nodes in the right hilum, thoracic inlet, mediastinum, and right axilla concerning metastatic disease. Brain magnetic resonance imaging (MRI) did not show intracranial metastatic disease. Next-generation sequencing (NGS) showed high tumor mutational burden (TMB) with no other targetable mutations. Given the low disease burden and patient's lack of interest in chemotherapy, the patient was started on single agent pembrolizumab with good treatment response. Seventeen months after initiating treatment, the patient presented to the clinic with worsening shortness of breath (SOB) which he noted a few months ago, was mild in the beginning, and has progressively gotten worse in the last few weeks. Most recent PET scan did not show any evidence of disease progression or signs of inflammation in lungs. An enlarged pulmonary artery diameter (PAD) measuring 35.96 mm with an aorta diameter (AoD) of 33.23 mm and PAD/AoD of 1.08 was shown in Figure 1, whereas PAD at the time of diagnosis was 31.67 mm, and AoD at the time of diagnosis was 33.92 mm, with a ratio of 0.93 as shown in Figure 2. Echocardiography (ECHO) was done, which showed normal left ventricular cavity size and ejection fraction of 55% with no regional wall motion abnormalities. Right ventricle (RV) cavity was markedly increased, with elevated right ventricular systolic pressure (RVSP) at 86 mm Hg with systolic pressure markedly elevated in pulmonary arteries consistent with severe PAH. No other significant abnormalities were found in aorta, tricuspid valve, mitral valve, and aortic valve, with mild regurgitation noted

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^aDepartment of Hematology/Oncology, Southern Illinois Health Cancer Institute, Carterville, IL, USA

^bDepartment of Nephrology, Southern Illinois Health, Carbondale, IL, USA

^cDepartment of Interventional Radiology, Cape Radiology Group Inc, Cape Girardeau, MO, USA

^dCorresponding Author: Lakshmi Manogna Chintalacheruvu, Department of Hematology/Oncology, Southern Illinois Health Cancer Institute, Carterville, IL 62918, USA. Email: lakshmikrishna365@gmail.com

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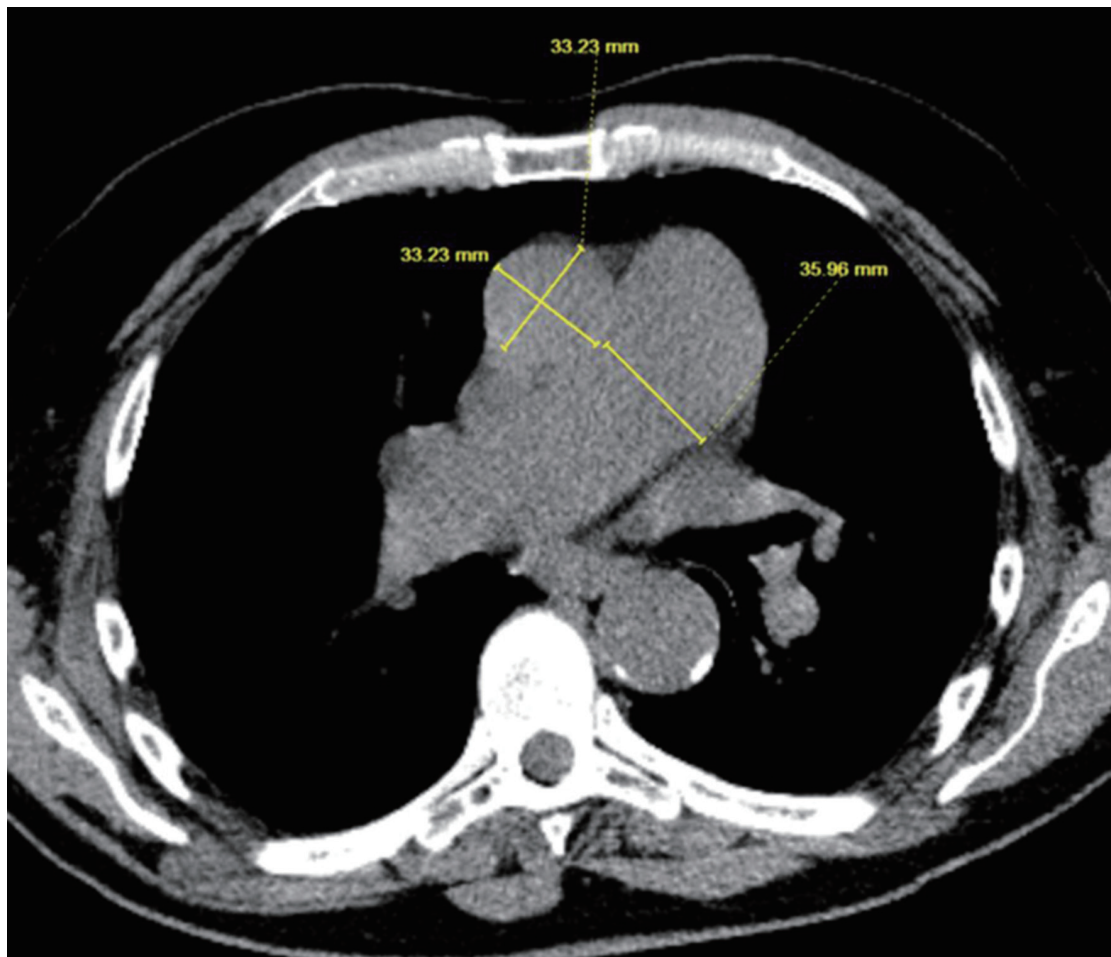


Figure 1. Imaging showing PAD and AoD after being on immunotherapy for 16 months. AoD: aorta diameter; PAD: pulmonary artery diameter.

at pulmonary valve with no structural abnormalities. Later, he underwent right heart catheterization which showed predominant precapillary PAH with elevated pulmonary artery systolic pressure (PASP) at 83 mm Hg (normal range: 18 - 25 mm Hg) with mean value of 58 mm Hg, pulmonary vascular resistance (PVR) of 10.5 Wood Units (WU) (normal range: 0.25 - 1.6 WU), and left ventricular end diastolic pressure (LVEDP) of 20 mm Hg (normal range: 4 - 12 mm Hg). Left main had 50% stenosis with patent left anterior descending artery, left circumflex, and right coronary arteries. Ventilation perfusion scan was within normal limits. Labs ordered for connective tissue and autoimmune disease were also within normal limits including antibodies against antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), Ku, Mi-2, OJ, PL-12, PL-7, signal recognition protein (SRP), U1 ribonucleoprotein (U1 RNP), U2 small nuclear ribonucleoprotein (U2 snRNP), Jo-1, cyclic citrullinated peptide (CCP), extractable nuclear antigen (ENA), fibrillarin, melanoma differentiation-associated 5 (MDA-5) P140, myeloperoxidase (MPO), NXP-2 P140, P155/140, polymyositis-scleroderma (PM-SCL), proteinase 3, and rheumatoid factor. He was evaluated by pulmonology. Given the overall clinical presentation with predominant

group 1 disease, immunotherapy-induced PAH was diagnosed as a more likely diagnosis of exclusion and pembrolizumab was discontinued. He was later started on riociguat and macitentan after which exertional fatigue and dyspnea improved. Repeated ECHO showed normal RV size. Later, the patient switched to single agent pemetrexed and is clinically tolerating treatments well with no evidence of disease progression. His overall exercise tolerance has improved.

Discussion

Pembrolizumab is an ICI that targets the PD-1 pathway, thereby activating T cells to attack cancer cells [2]. ICI-induced PAH is rare and the exact mechanism is unclear [2]. Diagnosis of PAH in cancer patients on immunotherapy can increase the mortality and morbidity [2]. Most of the cases diagnosed in the literature are based on diagnosis of exclusion as we do not have specific guidelines to diagnose and manage ICI-induced PAH [1]. This can lead to delayed diagnosis and can result in poor patient outcomes [1]. Pattern of PAH caused by ICI is through endothelial injury, thereby leading to group 1 precapil-

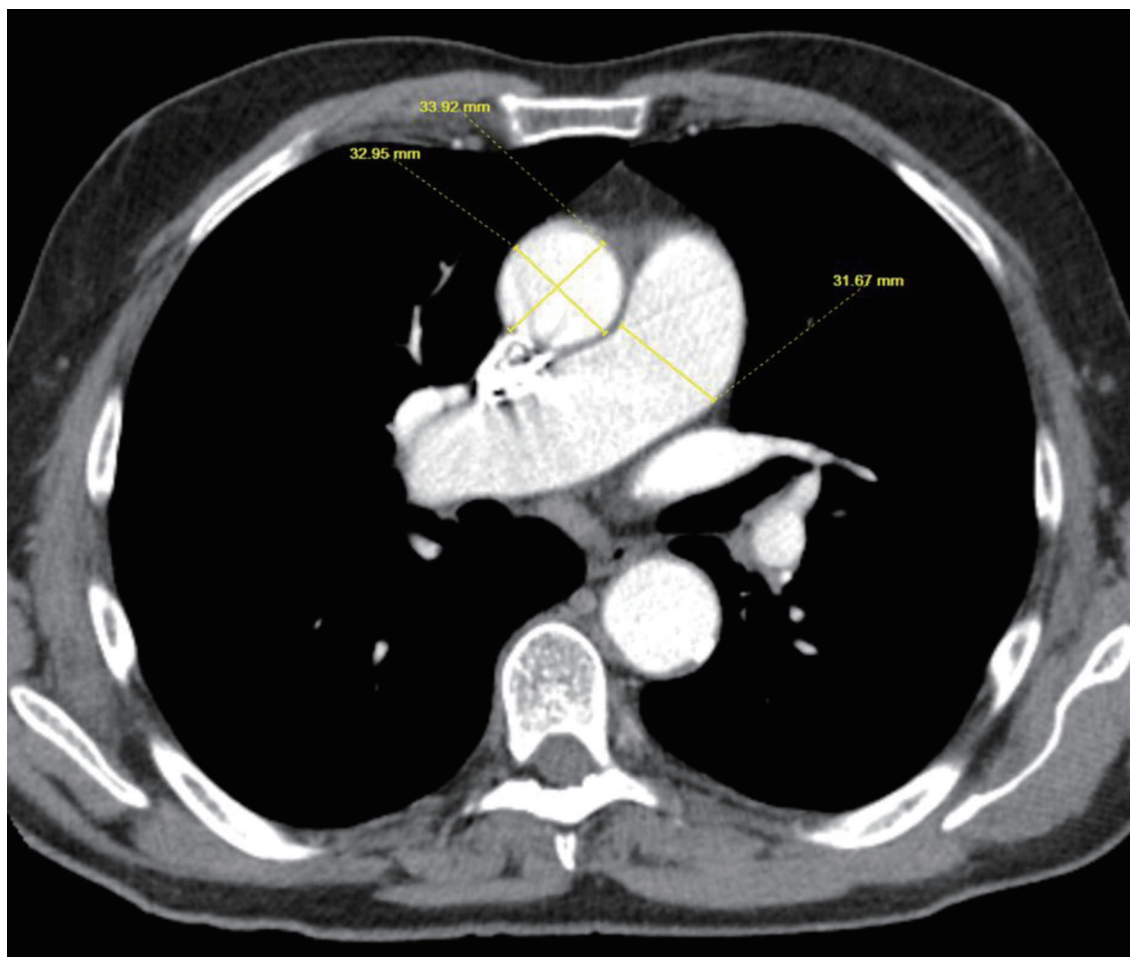


Figure 2. Image demonstrating PAD and AoD prior to initiation of immunotherapy. AoD: aorta diameter; PAD: pulmonary artery diameter.

lary type like in our patient [4].

Endothelial injury is more likely mediated by exaggerated immune response caused by immunotherapy leading to production of oxygen-free radicals causing tissue damage, endothelial dysfunction, and vasculitis [4]. Increased inflammation due to vasculitis leads to the loss of balance between vasoconstriction and vasodilation, thereby increasing the stiffness of pulmonary vasculature causing PAH [4].

In a retrospective study conducted by Palassin et al reviewing pharmacovigilance databases looking at PAH reported with ICI, they found 42 PAH cases among 73,032 ICI-associated adverse events with a fatality rate of 31% [1]. This shows the rarity and severity of PAH caused by ICI [1]. Among them, 50% are lung cancer patients and 22.2% are diagnosed with melanoma, with around 50% of them receiving nivolumab followed by pembrolizumab (14.3%) [1]. The median time to onset of symptoms of PAH was 77 days after the ICI treatment initiation [1]. Among patients diagnosed with PAH receiving ICI, 45% did not recover, 18% were recovering, and less than 10% patients recovered per their report [1]. The more likely explanation of high fatality rate is the failure to diagnose it early and no standard treatment guidelines available to treat

ICI-mediated PAH [1]. This signifies the importance of formulating guidelines for accurate diagnosis and timely treatment of PAH in this high-risk patient population [5]. Studies have shown that presence of a tumor will increase the expression of PD-L1 on cells, inhibition of which can promote the occurrence of more side effects at target organs [1]. So, there is a high likelihood of pulmonary toxicity in lung cancer patients compared to other solid tumors and these patients should be monitored closely compared to other solid tumors [1].

In another retrospective study conducted by Mylvaganam et al looking at the impact of ICI on pulmonary vasculature and right ventricular function, they found that ICI is associated with increased median PAD and AoD ratio from 0.83 to 0.89 ($P = 0.03$) and increased right ventricular free wall longitudinal systolic strain after a median exposure of 59 and 85 days, respectively [6]. There shows that ICI does have an impact on pulmonary vasculature and RV and severity might vary based on patient comorbidities [5].

Literature review has shown that PAD and PAD:AoD ratio is helpful in diagnosing PAH early [5]. In a retrospective study conducted by Zhao et al on lung cancer patients receiving nivolumab, they found that mean PAD has increased from

26.3 ± 2.8 mm versus 28.0 ± 3.0 mm ($P < 0.001$) pre- and post-treatment respectively and two patients had life-threatening complications due to PAH, both showing post-treatment PAD:AoD ratio > 1 [4]. So, these studies reinforce the significance of monitoring computed tomography (CT) scan and ECHO findings to closely monitor PAD and AoD to identify early cases of PAH to decrease morbidity and mortality [4]. More research needs to be done to find out which factors contribute to the PAH progression and its severity [4].

Apart from discontinuing ICI, no specific guidelines exist for management of ICI-induced PAH. Our patient got started on riociguat and macitentan. Riociguat is a guanylate cyclase stimulator and has been known to improve PVR, exercise tolerance, and brain natriuretic peptide (BNP) levels [7]. Macitentan is an endothelin receptor antagonist approved by Food and Drug Administration (FDA) for PAH [8]. Most of the tumors secrete excess fibrous tissue through fibroblasts to prevent the entry of T cells, thereby creating an immune-excluded tumor environment [8]. In a study conducted by Son et al where they created macitentan nanoparticles and repositioned them in the tumor microenvironment (TME), they found that these nanoparticles regulate the expression of fibroblasts and decrease fibrotic progression of tumor cells and also decrease the activity of cancer cells derived exosomes, thus modulating the TME and regulatory T (Treg) cells and maintaining good balance between ICI-mediated tumor response and its toxicity [8]. Interleukin (IL)-12 and IL-17 also play a role in inflammatory-mediated PAH and B-cell depletion with rituximab has been known to decrease IL-12 and IL-17 levels predictive of favorable response to the drug [9]. More studies are needed to explore the role of rituximab and other immunosuppressive agents in early treatment of PAH to avoid further vascular damage [9].

Imbalance in gut bacteria composition is known to happen in cancer patients. This allows increased pathogenic bacterial product translocation from the gut into systemic circulation and increases trimethyl N-oxide and serotonin [10]. This aggravates peripulmonary vascular inflammation, endothelial dysfunction, and worsening of PAH [10]. This raises a question to see if there is any role of fecal microbiota transplantation (FMT) where functional bacteria from healthy donor feces is transferred to patients to repair gut dysbiosis in improving outcomes in PAH [10]. To answer this question, there is a clinical trial being conducted to evaluate the efficacy of FMT in treating PAH [11]. It might be hard to conduct a specific study looking at the role of FMT in treating ICI-induced PAH due to the small number of patients, but if the above study shows positive results, it is worth applying those results to treat ICI-induced PAH.

Conclusion

PAH due to ICI is a less common side effect with high fatality rate. Most of the time, it is a diagnosis of exclusion and given the rarity of the disease, no specific diagnostic and treatment guidelines exist. Early detection by closely monitoring PAD and AoD to identify PAH in patients receiving ICI is essential to avoid severe cardiovascular complications. Apart from

vasodilators, the role of immunosuppression such as steroids and rituximab needs to be explored. More studies are needed to determine the role of FMT in treating PAH due to ICI.

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Conflict of Interest

The authors declare that they do not have a conflict of interest.

Informed Consent

Informed consent has been obtained.

Author Contributions

Lakshmi Manogna Chintalacheruvu: corresponding author, helped in framing the concept, diagnosis management, literature review, editing, and primary manuscript drafting. Vamsi Krishna Chilluru: data collection literature review and manuscript editing. Narendra Babu Gutta: radiological analysis image preparation and manuscript editing. All authors reviewed and approved final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

AoD: aorta diameter; BNP: brain natriuretic peptide; CT: computed tomography; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; ECHO: echocardiography; FDA: Food and Drug Administration; FDG: F-fluorodeoxyglucose; FMT: fecal microbiota transplantation; ICIs: immune checkpoint inhibitors; LN: lymph node; MRI: magnetic resonance imaging; NGS: next-generation sequencing; PAD: pulmonary artery diameter; PAH: pulmonary arterial hypertension; PD-1: programmed cell death-1; PD-L1: program cell death-ligand 1; PASP: pulmonary artery systolic pressure; PET: positron emission tomography; RV: right ventricle; RVSP: right ventricular

systolic pressure; SOB: shortness of breath; TMB: tumor mutational burden; TME: tumor microenvironment

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