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CASE REPORT

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Use of combined chemotherapy and immunotherapy improves pulmonary arterial hypertension

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Abstract

Treatment modalities for pulmonary arterial hypertension (PAH) improve quality of life and walk distance. However, none of these therapies alter the structural/functional pulmonary vascular integrity that results in vascular remodeling. PAH smooth muscle cells share biological characteristics with cancer cells, which may be potential therapeutic targets for PAH. We present a case of a patient with connective tissue disease (CTD)-associated PAH treated on triple therapy who developed metastatic lung adenocarcinoma. While on PAH triple-therapy, she received a combination of carboplatin, pemetrexed, and pembrolizumab. She eventually had a complete pathologic response, no evidence of cancer recurrence, and significant improvement of PAH/overall clinical status. After discontinuation of neoplastic therapy, her clinical status worsened, she eventually passed away, and lung biopsy findings revealed evidence of severe pulmonary smooth muscle cell hypertrophy and pulmonary veno-occlusive disease. This report suggests that combined chemotherapy and immunotherapy may influence the efficacy of PAH therapies and improve clinical status.

KEYWORDS
carboplatin, connective tissue disease, pembrolizumab, pemetrexed, pulmonary arterial hypertension

INTRODUCTION

Therapies for pulmonary arterial hypertension (PAH) include vasodilators, such as endothelial receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs that improve walk distance, functional status and may influence quality of life.[1] However, none of these therapies are known to alter the structural or functional pulmonary vascular integrity that forms plexiform lesions and vascular remodeling. Pulmonary artery smooth muscle cells (PASMCs) share biological characteristics with tumor cells, including insensitivity to growth suppression,

Abbreviations: BET, bromodomain and extra terminal protein; CI, cardiac index; CO, cardiac output; CRT+IO, chemotherapy+immunotherapy; CTD, connective tissue disease; HR, heart rate; ILD, interstitial lung disease; LA, left atrium; LV, left ventricle; PAH, pulmonary arterial hypertension; PASMC, pulmonary arterial hypertension smooth muscle cells; PASP, pulmonary artery systolic pressure; RA, right atrium; RAP, right atrial pressure; RV, right ventricle; SV, stroke volume.

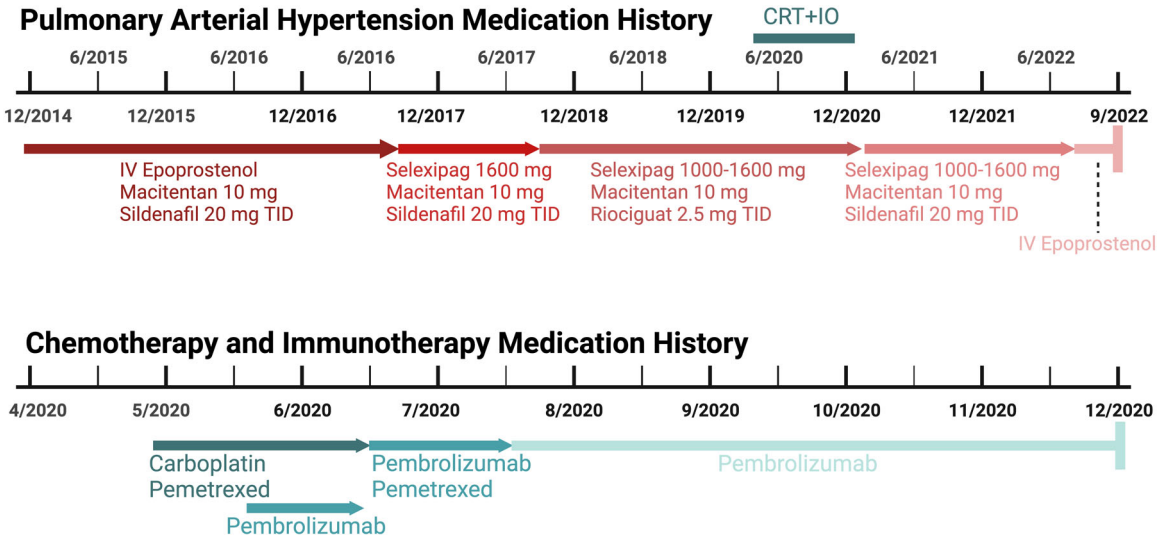

FIGURE 1 Time of treatment course for pulmonary arterial hypertension with a timeline for chemotherapy and immunotherapy (CRT + IO) course for concomitant lung adenocarcinoma treatment. Figure created with Biorender.com.

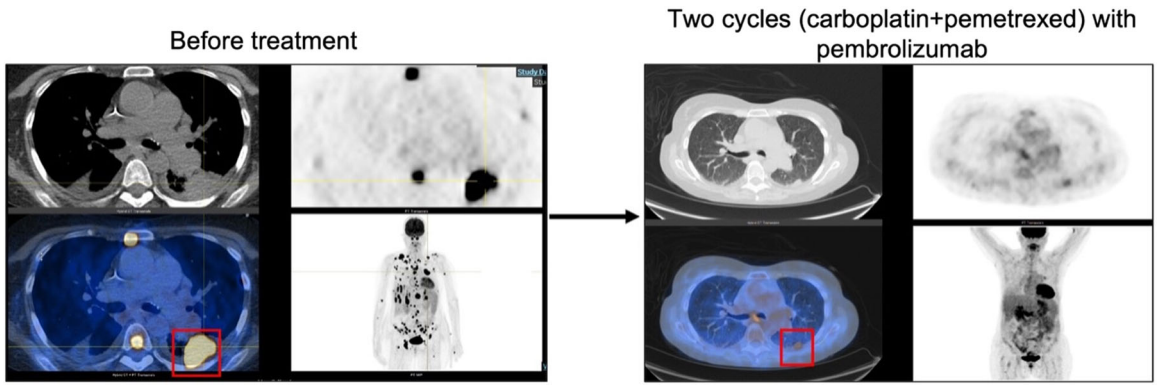

FIGURE 2 PET/CT imaging revealed a 4 cm lesion (46 SUV) in the posterior aspect of the superior segment of the left lower lobe with multiple hypermetabolic lesions in the liver (largest 2.8 cm, 43 SUV), and widespread osseous disease. After two cycles of carboplatin +pemetrexed (pembrolizumab added in Cycle 2), the lung lesion decreased in size to 1.3 cm (2.7 SUV), and there was no more presence of metastatic disease. The red outline indicates a primary lung adenocarcinoma lesion.

TABLE 1 Right heart catheterization measurements during the treatment course.

	12/15/14	12/5/15	6/28/17	5/23/19[a]	2/4/21	11/2/21	4/20/22
RA pressure (mmHg)	20	20	9	10	4	20	8
Mean PA pressure (mmHg)	54	54	30	32	49	53	58
Mean PCWP	16	12	15	15	12	16	18
Cardiac output (L/min)	3.11	3.12	4.27	4.66	4.57	3.11	2.41
Pulmonary vascular resistance (WU)	12	13	4	4	8	12	17

[a]CRT + IO therapy from May 2020 to November 2020.

resistance to apoptosis, deregulated cellular metabolism, sustained proliferative signaling, immune evasion, and genome instability.[2] The mechanisms that contribute to plexiform lesions and multiple other cell types in PAH may overlap with mechanisms that contribute to neoplastic lesions in malignancy. Treatments that target these pathways and mechanisms are under active investigation.

CASE REPORT

A 52-year-old female with a history of connective tissue disease (CTD)-associated PAH, CREST syndrome, interstitial lung disease, and ulcerative colitis presented to a local outside hospital with a chief complaint of shortness of breath, fatigue, and bone pain. She received triple therapy for PAH, as outlined in Figure 1. During her workup, CT chest and PET imaging revealed enlarged mediastinal nodes, bilateral ground glass interstitial opacities with areas of septal thickening, an incidental 4 cm left lower lobe nodular mass, multiple hypermetabolic lesions in the liver (largest 2.8 cm, 43 SUV) and osseous metastatic disease. A US-guided biopsy showed poorly differentiated metastatic lung adenocarcinoma (Stage 4) with 5% tumor cells expressing PD-L1 and negative for *EGFR/ALK* gene alterations. Pembrolizumab with carboplatin and pemetrexed were considered as first-line therapy for this cancer.[3] However, due to a concern that immunotherapy may exacerbate interstitial lung disease and scleroderma, she was started on carboplatin and pemetrexed, which she tolerated well after one cycle (cycle = treatment every 3 weeks). Pembrolizumab was added to the treatment regimen at Cycle 2.

PET/CT scan post-cycle 2 revealed near interval complete response with lower lung lobe mass decreasing in size and complete resolution of widespread metastatic disease (Figure 2). Her treatment course was complicated by chemotherapy-induced pancytopenia, dyspnea, and fatigue. As a result, in later treatment, she only received pembrolizumab. She received single-agent pembrolizumab for another 5 months until treatment was discontinued due to pneumonitis and no evidence of active malignancy on PET/CT imaging. Repeated surveillance PET/CT imaging showed no evidence of cancer recurrence or metastatic disease for 18 months of follow-up. Right heart catheterizations, clinical parameters, and echocardiogram reads are in Tables 1–3.

PAH TREATMENT COURSE

During her diagnosis of lung adenocarcinoma, she received PAH triple therapy along with chemotherapy +immunotherapy (CRT + IO) (Figure 1).

TABLE 2 REVEAL Lite 2 score and clinical parameters.

Parameters	12/15/14	7/15/15	4/25/16	3/14/17	5/22/18	5/21/19	4/26/20	6/17/20	9/3/20	11/5/20	2/3/21	12/1/21	4/21/22	8/19/22
BNP (pg/mL)	1337	114	229	111	131	281	282	699	413	851	1081	>5000	>5000	>5000
6-minute walk test	285	262	363	365	359	360	–	410	280	–	263	301	292	–
NYHA/WHO classification	3	3	2	2	2	2	2	1	1	1	2	3	3	4
Systolic blood pressure	155	121	100	112	102	107	104	100	110	92	94	94	105	108
Heart rate (beats/min)	107	105	84	99	104	106	100	92	96	95	98	98	76	74
eGFR < 60 mL/min/1.73 m^2 or renal insufficiency	No	No	No	No	No	No	No	No	No	No	No	No	No	No
REVEAL Lite 2 score	9	8	7	6	7	8	–	6	6	–	10	10	11	–
DLCO % Pre of predicted	–	–	–	–	52.3	46.3	–	23.9	29.3	32.6	27.4	28.7	24.4	–
FVC % Pre of predicted	72.5	73.2	85.9	87	83.2	81.7	–	70.8	70.9	70.7	68.1	66.4	65.6	–

TABLE 3 Echocardiogram reads during the treatment course.

Parameter	12/3/14	7/15/15	4/25/16	3/14/17	5/22/18	5/21/19	4/26/20	6/17/20	9/3/20	11/5/20	2/3/21	12/1/21	4/21/22	8/19/22
LV size/EF	Normal, EF 55–60	Normal/EF 65%–69%	Normal/ EF > 70%	Normal/ EF > 65% –69%	Normal/ EF > 70%	Normal/ EF > 70%	Normal/ EF > 70%	Normal/ EF > 70%	Normal/ EF > 70%	Normal/ EF > 70%	Small/ EF > 70%	Small/ EF > 70%	Small/ EF > 70%	Extremely small/ EF > 70%
RV	Severely enlarged, mod to severely depressed function	Normal, hypokinetic wall	Normal size and function	Mildly enlargement/ moderate depressed function	Normal size and function	Mildly enlarged/ mild-to-moderate depressed function	Normal size and function	Size unknown/normal function	Normal/ mild depressed function	Mildly enlarged/ mild depressed function	Severely enlarged/ moderately depressed function	Mildly enlarged/ depressed function	Moderate to severely enlarged/ moderate to severely depressed function	Severely enlarged/ moderately depressed function
RA	Enlarged	Normal	Moderately enlarged	Mildly enlarged	Normal size	Enlarged size	Normal size	---	Normal size	Normal size	Enlarged size	Moderately enlarged	Enlarged size	Mildly enlarged
LA	Normal	Mildly enlarged	Moderately enlarged	Mild to moderately enlarged	Normal size	Moderately to severely enlarged	Moderately enlarged	Enlarged size	Moderately enlarged	Normal size	–	Enlarged	Moderately enlarged	Moderately enlarged
Pericardial effusion	Moderate circumferential (pericardial window was done)	No	No	Trace, posterior	No	Trace, posterior	Small, posterior	Trace, posterior	Small, anterior, and posterior	No	Small, anterior, and posterior	Small, postero-lateral	Small, anterior, and posterior	Trace, posterior
PASP (mmHg)	81–86	Insuff TR jet	Insuff TR jet	69	Insuff TR jet	Insuff TR jet	Insuff TR jet	Insuff TR jet	Insuff TR jet	47	94	85–90	69	94–99
RAP (mmHg)	5–10	5	<5	<5	<5	5	5	<5	5	10	20	15–20	20	5–10
HR		89	99	89	90	77	120	81	87	124	98	77	70	71

TABLE 3 (Continued)

Parameter	12/3/14	7/15/15	4/25/16	3/14/17	5/22/18	5/21/19	4/26/20	6/17/20	9/3/20	11/5/20	2/3/21	12/1/21	4/21/22	8/19/22
SV (mL)	30.13	34.6	48.7	48.7	78	76.4	Sub-optimal quality	74	80	76	58	66	48.8	33.4
CO (L/min)	3.01	3.1	6.3	4.3	7	5.9	Sub-optimal quality	6	7	9.4	5.9	5.1	3.4	2.4
CI (L/min/m^2)	1.57	1.6	3.4	2.3	3.8	3.3	Sub-optimal quality	3.4	4.1	5.6	3.4	3	2.1	1.6

Abbreviations: CI, cardiac index; CO, cardiac output; HR, heart rate; LV, left ventricle; PASP, pulmonary artery systolic pressure; RA, right atrium; RAP, right atrial pressure; RV, right ventricle; SV, stroke volume.

After 1 month of neoplastic and PAH therapies, she returned to pulmonary clinic with no symptomatic concerns. Pulmonary function tests (PFTs) revealed unchanged FEV1/FVC ratios, but a decrease in DLCO from 46.9% to 23.9% predicted (Table 2). Her 6-minute walk distance (6MWD) improved with functional class I symptoms, and she returned to work as a teacher. Right heart catheterization was deferred at that time due to patient preference (Table 1). She improved clinically at rest/exertion for another 6 months. Echocardiograms showed an improvement in cardiac output/cardiac index, a normal right atrium size, and mild depressed right ventricular (RV) function (Table 3). Furthermore, her REVEAL Lite 2 score decreased from eight to six while she was receiving a combination of PAH triple therapy and immunotherapies (Table 2 and Figure 3). The decrease in tumor burden combined with hemodynamic improvement was associated with improvement in her clinical symptoms.

After immunotherapy was discontinued, she continued PAH triple therapy for 21 months, but her disease worsened; mean pulmonary arterial pressure and pulmonary vascular resistance were elevated, and cardiac output was reduced. B-type natriuretic peptide levels were elevated to >5000 pg/mL, the 6-min walk test showed a decrease from 410 to 292 m, functional class worsened, and REVEAL Lite 2 risk stratification scores were elevated (Figure 3). Echocardiograms showed severe RV enlargement and moderately depressed RV function.

In January 2021, the patient persisted with PAH triple therapy, yet experienced poor tolerance to riociguat, leading to a switch to sildenafil, which she tolerated more effectively (Figure 1). Her clinical condition

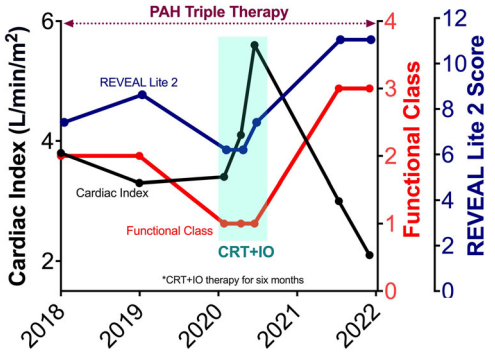

FIGURE 3 Time course of clinical status and hemodynamics before and after initiation of combined chemotherapy and immunotherapy (CRT + IO). The horizontal dashed line represents the time when the patient received PAH triple therapy, and the light blue highlighted region indicates the time when CRT + IO therapy was incorporated for the treatment of metastatic lung adenocarcinoma. PAH, pulmonary arterial hypertension.

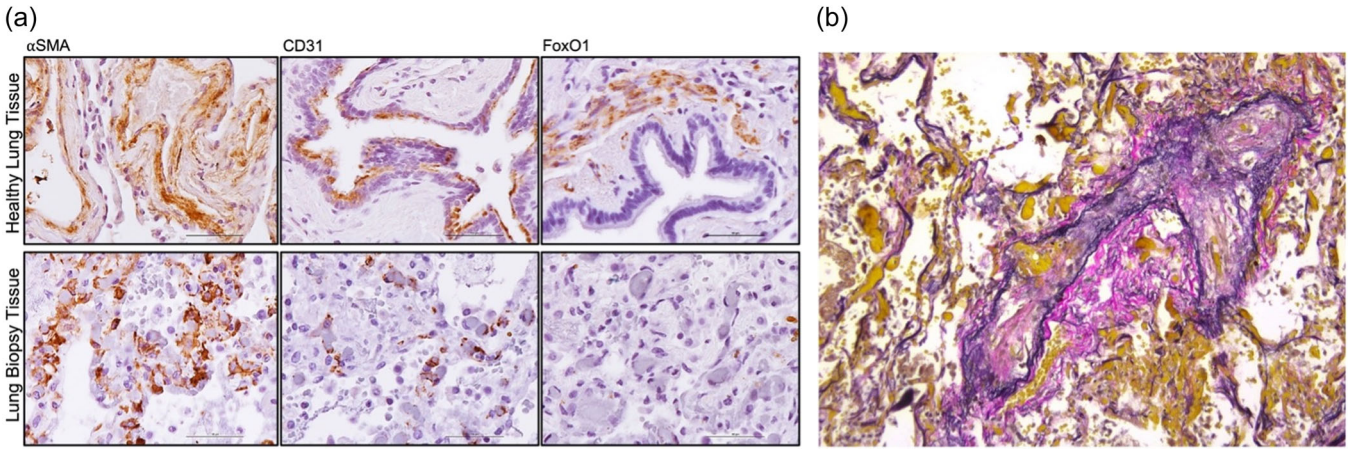

FIGURE 4 (a) Immunohistochemical staining of lung biopsy tissue from case compared to healthy lung tissue control for mesenchymal marker α-smooth muscle actin, endothelial marker CD31, and transcription factor Fox01. (b) VVG stain of lung biopsy tissue showing a pulmonary vein in an interlobular septum with fibrous obliteration of the lumen. Black staining indicates elastic fibers, pink-purple stain indicates fibrous tissue and gold staining indicates red blood cells. ×200 magnification.

continued to worsen from April to September 2022, and despite switching to intravenous epoprostenol to improve symptoms, she passed away in September 2022 from acute on chronic respiratory failure and severe right-sided heart failure. An autopsy of the lung revealed severe PASMCs hypertrophy, interstitial lung disease, and no evidence of pulmonary thromboembolism, infectious pneumonia, residual primary/metastatic disease, or lymphangitic carcinomatosis.

Verhoeff-Van Gieson and immunohistochemical staining of the lung tissue biopsies showed fibrous occlusion of the pulmonary vein in an interlobular septum, indicating pulmonary veno-occlusive disease (PVOD). There was a corresponding increase in tissue expression of α-SMA, with a decrease in CD31 and FOXO1 (Figure 4).

DISCUSSION

CRT + IO may augment the efficacy of PAH triple combination therapy and improve the clinical status of a patient with CTD-associated PAH. Several antineoplastic therapies used in the treatment armamentarium for oncology have been evaluated in the preclinical and clinical setting for PAH, including tyrosine kinase inhibitors, taxanes (paclitaxel), BET bromodomain inhibitors, and monoclonal antibodies.[4–10] A proposed mechanism for how CRT + IO induces a reversal of PAH may be that treatment increased expression of FOXO1 transcription factor in PAMSCs, leading to increased apoptosis and BMPR2 signaling, and reduced cell proliferation. FOXO1 is implicated as a critical proapoptotic, antiproliferative, and antimetastatic marker in various neoplasms, including NSCLC and in pulmonary hypertension (PH).[11,12] In various cancer models, FOXO1 has been shown to inhibit TGFβ-induced epithelial-to-mesenchymal transition (EMT), rendering enhanced epithelization of cancer cells, reduced metastatic capacity, and likely increased chemosensitivity.[13,14] We theorize that this reverse remodeling modulated by FOXO1 that is exhibited in cancer cells may be present in PASMCs. Though there are a few studies suggesting that chemoimmunotherapy may influence remodeling,[15,16] we cannot conclude about the individual influence of pembrolizumab, pemetrexed, and carboplatin on this mechanism of reversal remodeling.

In our study, end-of-treatment lung biopsies showed PVOD with corresponding worsening of PAH, as shown by decreased expression of FOXO1. It is possible that during the phase of improved pulmonary function while on CRT + IO and triple therapy, there was an associated increase in FOXO1, enhanced endothelization, and increased apoptosis of PASMCs.[17]

The tissue biopsy findings suggest that discontinuation of CRT + IO accelerated PAH disease course, as shown by decreased expression of FOXO1 at end biopsy. However, it is also possible that CRT + IO worsened her PAH by inducing PVOD and there may have been a change in the phenotype of the PAH disease.

The lung biopsy showed evidence of PVOD, a rare subtype of PH that is characterized by obstruction of small pulmonary veins, particularly intimal fibrosis of preseptal veins.[18] The etiology of PVOD is unclear but has been associated with *EIF2AK4* genetic mutations, viral infections, hematological malignancies, bone marrow and stem cell transplantation, chemotherapies, and autoimmune and CAD disorders.[19,20] Though there is an

association between PVOD and chemotherapy, the mechanistic relationship is still unclear. Alkylating agents, in particular cyclophosphamide, have been implicated in inducing PVOD and this may be mediated by oxidative damage.[21] In this particular case, we can also speculate that this patient had underlying PVOD associated with scleroderma, combined chemo/immunotherapy may have halted its disease progression, and its withdrawal exacerbated her condition.

Due to the combined nature of chemo- and immunotherapy in this case, it is difficult to clearly delineate the individual roles of these antineoplastic therapies on CTD-associated PAH. Future clinical investigation is warranted to evaluate antineoplastic therapies and their influence on reversing PAH.

AUTHOR CONTRIBUTIONS

Tejaswini P. Reddy and Zeenat Safdar wrote the original draft of the manuscript. Tejaswini P. Reddy, Roberto Barrios, Wei Qian, and Zeenat Safdar edited the figures and tables. All authors reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The authors of this manuscript obtained appropriate permission and consent to publish this case report.

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