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CASE REPORT

ADVANCED

CLINICAL CASE SERIES

# Malignancy-Related Pulmonary Hypertension Presenting as a Pulmonary Veno-Occlusive–Like Syndrome

## A Single-Center Case Series

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**ABSTRACT**

Tumoral obstruction is a small, but broadly defined, category of pulmonary hypertension that encompasses microvascular tumor emboli, tumor thrombotic microangiopathy, and macrovascular tumor obstruction within the pulmonary circulation. We present 4 patients with solid tumors, severe pre-capillary pulmonary hypertension, right ventricular failure, and pulmonary veno-occlusive–like disease. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:1044–50)
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Tumor-related pulmonary hypertension (PH) can arise from different types of malignancy and from tumor-related obstruction within any compartment of the pulmonary vascular bed.

**LEARNING OBJECTIVES**

- Cancer-associated pulmonary hypertension can present with vague symptomatology and rapidly progress to death.
- Early clinical diagnosis is critical; therefore suspicion for this disease process is essential to detecting it.
- Pulmonary hypertension targeted therapy may worsen clinical status.

Obstruction can be caused by microvascular tumor emboli, thrombotic microangiopathy, or macrovascular obstruction (in situ or embolic) within the pulmonary circulation (1). Patients present in different ways based on the mechanism of pulmonary artery obstruction, location, and type of malignancy. Presentations can be acute, with severe cardiopulmonary compromise, making definitive antemortem diagnosis elusive. A natural consequence is under-recognition of PH directly arising from malignancy and a lack of understanding of how these patients present. We report on 4 patients with different forms of malignancy, with rapid-onset severe pre-capillary PH, right ventricular (RV) failure, and clinical course mimicking pulmonary veno-occlusive disease (PVOD) (**Figure 1, Table 1**).

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## CASE DESCRIPTIONS

**CASE 1.** A 65-year-old man presented with hypotension and dyspnea. A transthoracic echocardiogram (TTE) demonstrated severe PH and RV dysfunction. His medical history included stage IV lung adenocarcinoma, end-stage renal disease, controlled hypertension, atrial fibrillation (AF), and coronary artery disease. He was diagnosed with primary lung adenocarcinoma with subsequent left lung lobectomy 9 years earlier; surveillance computed tomography (CT) 2 years afterwards revealed a relapse with bilateral lung nodules, and he was started on chemotherapy (carboplatin, gemcitabine, and pembrolizumab) 7 months later. Examination on admission revealed an oxygen saturation of 95% on 5 l/min of supplemental oxygen, an irregularly irregular rhythm, jugular venous pressure 25 cm of water, and bilateral lower extremity edema. Chest radiograph showed pulmonary edema and bilateral pleural effusions. TTE revealed severe RV dilation and dysfunction, with Doppler evidence consistent with markedly elevated pulmonary vascular resistance (PVR) and normal left atrial pressure (LAP) (Figure 2). A CT chest scan revealed a dilated pulmonary artery with multiple bilateral lung nodules. Based on the severity of his pre-capillary PH, severe airspace disease, and diffuse pulmonary edema, his diagnosis was highly consistent with PVOD. Oncology did not deem him a candidate for additional chemotherapy. No pulmonary vasodilators were started due to the high probability of post-capillary venous obstruction as the mechanism of his PH. The patient expired due to progression of hypoxia within 48 h.

**CASE 2.** A 74-year-old woman presented with 3 weeks of progressive dyspnea. She had a TTE reporting "PH and RV failure." She was treated with intravenous (IV) epoprostenol and sildenafil. Her medical history included breast cancer and AF. Her cancer was diagnosed 20 years earlier and was only treated with radiation. On transfer to our institution, she presented with an irregular tachycardia of 124 beats/min, an oxygen saturation of 80% on 20 l/min of high-flow nasal cannula at a fraction of inspired oxygen of 100%, and with decreased breath sounds. Ultrasound and ventilation/

### ABBREVIATIONS AND ACRONYMS

**AF** = atrial fibrillation

**CT** = computed tomography

**CTEPH** = chronic thromboembolic pulmonary hypertension

**IV** = intravenous

**LAP** = left atrial pressure

**PH** = pulmonary hypertension

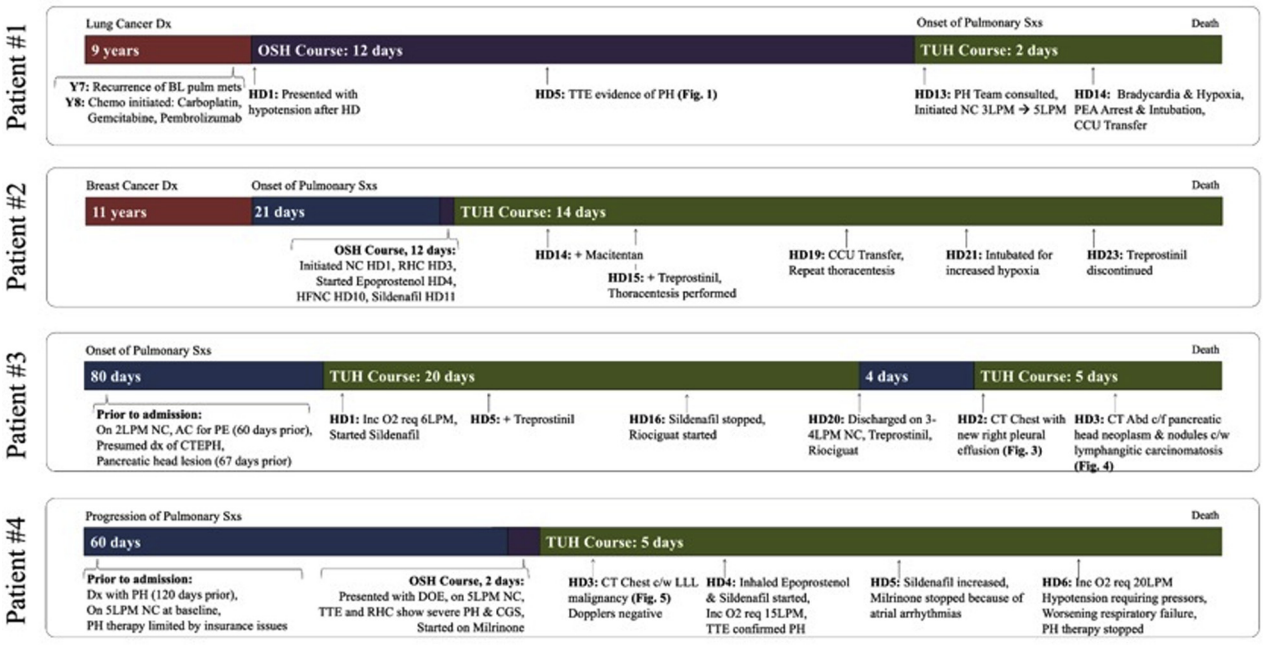
**PVOD** = pulmonary veno-occlusive disease

**PVR** = pulmonary vascular resistance

**RV** = right ventricle

**TTE** = transthoracic echocardiogram

**FIGURE 1** Timeline of the 4 Study Cases



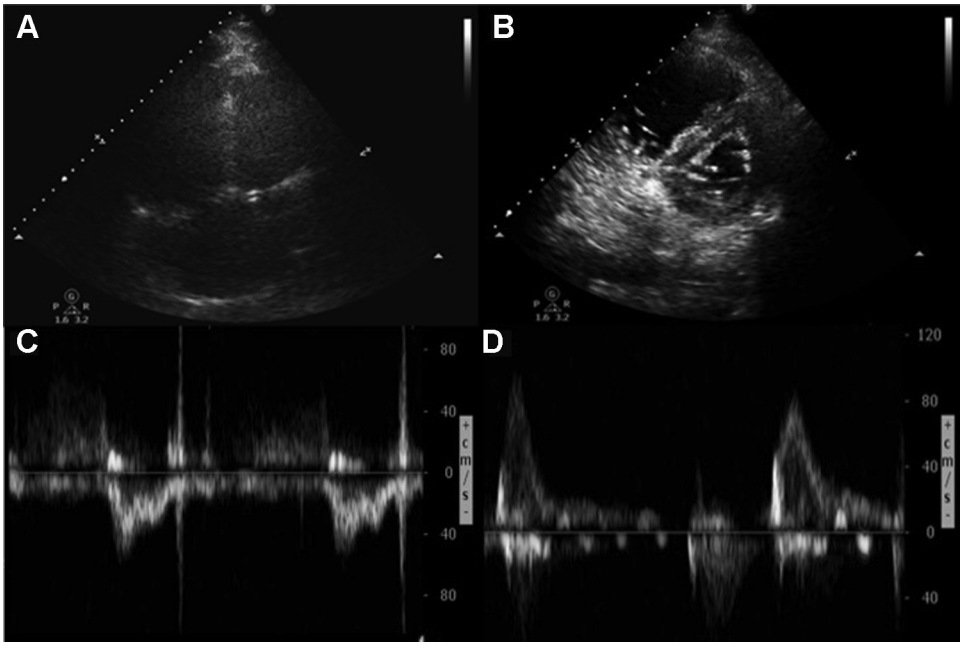

AC = anticoagulant agent; BL pulm mets = bilateral pulmonary metastasis; CCU = cardiac care unit; c/f = concerning for; CGS = cardiogenic shock; CT = computed tomography; c/w = consistent with; DOE = dyspnea on exertion; Dx = diagnosis; HD = hospital day; HFNC = high-flow nasal cannula; LLL = left lung lobectomy; LPM = liters per minute; NC = nasal cannula; PE = pulmonary embolism; PEA = pulmonary endarterectomy; PH = pulmonary hypertension; RHC = right heart catheterization; Sxs = signs and symptoms; TTE = transthoracic echocardiogram; TUH = Temple University Hospital.

**TABLE 1 Comparison Between Study Cases Lung, Breast, and Pancreatic Cancer**

| | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| Age, y/sex | 65 M | 74 F | 47 F | 77 M |
| Type of primary cancer | Lung (adenocarcinoma) | Breast | Pancreatic (adenocarcinoma) | Lung (primary bronchogenic carcinoma) |
| Clinical presentation | Dyspnea and hypotension | Dyspnea on exertion and hypoxia | Dyspnea on exertion, fatigue, orthopnea, cough, anorexia | Dyspnea on exertion, chest pain |
| Hemodynamic parameters | No right heart catheterization available | RA: 12 mm Hg<br>RV: 107/10 mm Hg<br>PA: 110/30/64 mm Hg<br>PCWP: 15 mm Hg<br>PVR: 11 WU<br>CI: 1.65 l/min/$m^2$ | RA: 11 mm Hg<br>RV: 61/18 mm Hg<br>PA: 68/32/45 mm Hg<br>PCWP: 6 mm Hg<br>PVR: 13 WU<br>CI: 1.75 l/min/$m^2$ | RA: 21 mm Hg<br>RV: 79/9 mm Hg<br>PA: 62/30/43 mm Hg<br>PCWP: 10 mm Hg<br>PVR: 10 WU<br>CI: 1.7 l/min/$m^2$ |
| Pathology | None | None | (see Figure 5) | None |
| PH-therapy | None | Sildenafil, epoprostenol, treprostinil, macitentan | Treprostinil, riociguat | Sildenafil, epoprostenol |
| Anticoagulation | Prophylactic heparin | Therapeutic heparin | Therapeutic heparin | Therapeutic heparin |
| Cancer to PH diagnosis (see Figure 1) | PH diagnosed 9 yrs after cancer diagnosis | PH diagnosed 11 yrs after cancer diagnosis | PH diagnosed 2 months after cancer Ca detected | PH diagnosed 4 months before cancer detected |
| PH diagnosis to death (see Figure 1) | PH to death within 9 days | PH to death within 23 days | PH to death within 29 days | PH to death within 4 months |

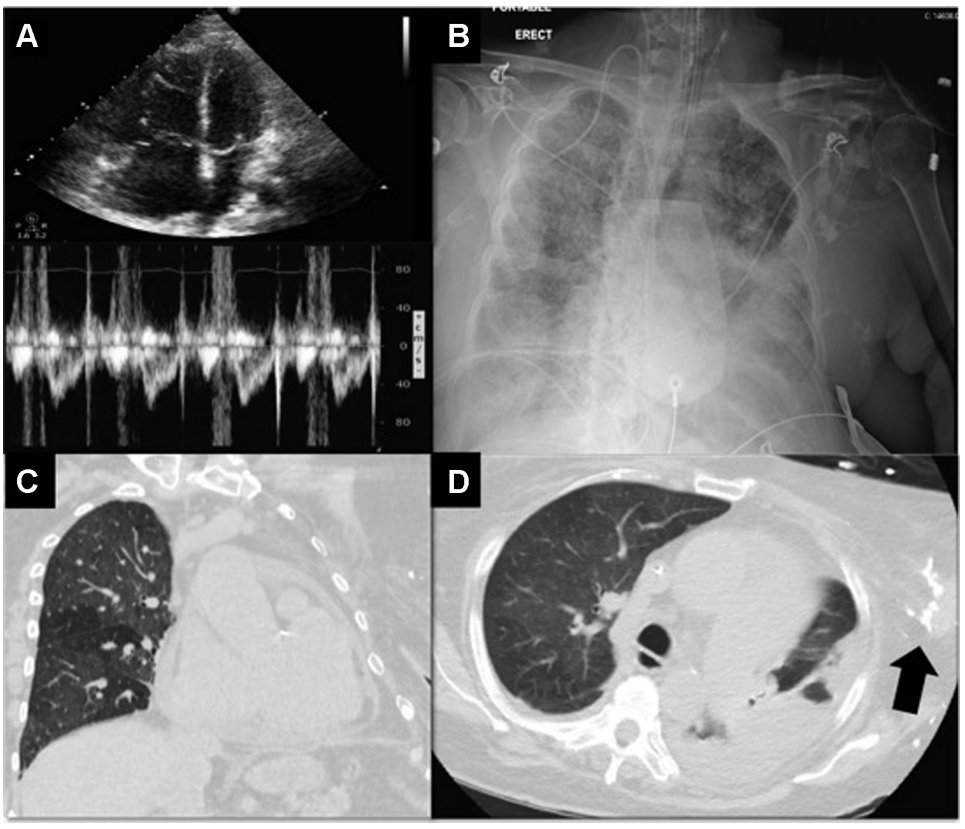
CI = cardiac index; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RA = right atrium; RV = right ventricle; WU = Wood units.

**FIGURE 2 Case 1**




**(A)** Transthoracic echocardiogram showing severe right atrial dilation, right ventricular (RV) dilation, and RV dysfunction. **(B)** Transthoracic echocardiogram showing flattening of interventricular septum during end-systole. **(C)** Transthoracic echocardiogram showing high pulmonary vascular resistance with mid-systolic notch pattern. **(D)** Transthoracic echocardiogram showing mitral E/A ratio consistent with normal left atrial pressure.

**FIGURE 3** Case 2

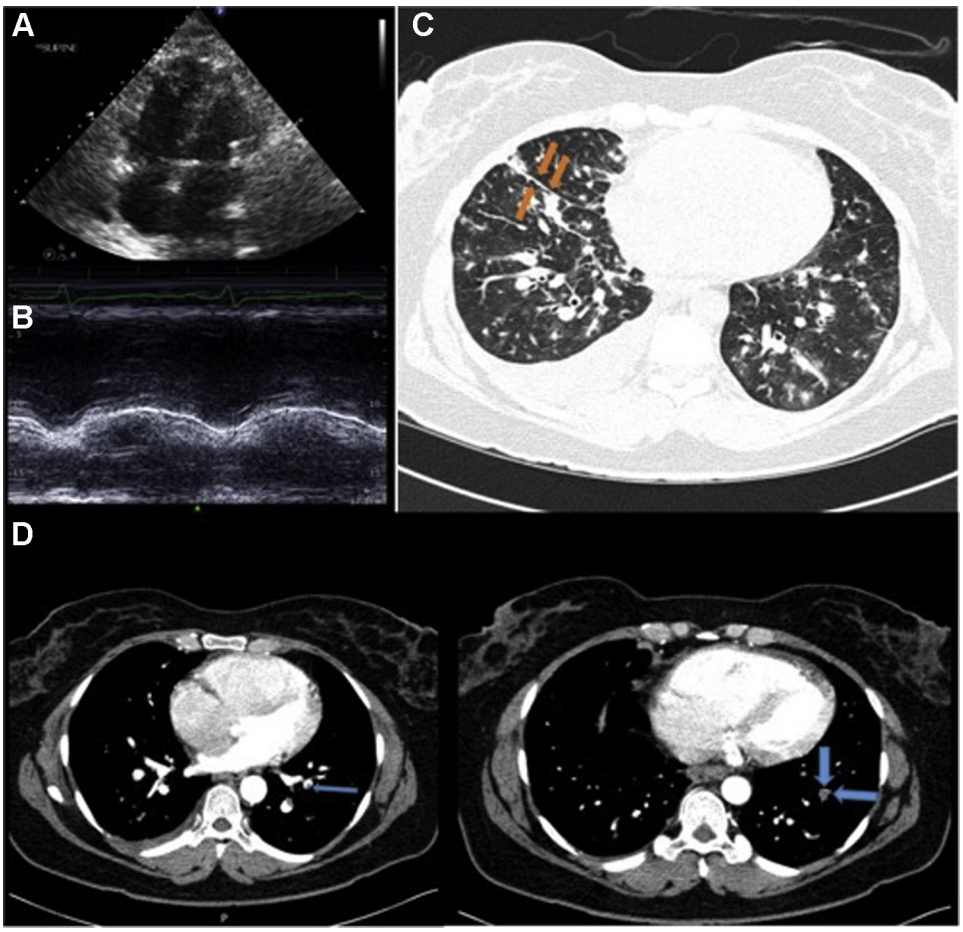



**(A)** Transthoracic echocardiogram showing right ventricular (RV) hypertrophy, moderate RV dysfunction, and moderate to severely enlarged apex-forming configuration. RV outflow tract pulse wave Doppler notching and reduced acceleration time. **(B)** X-ray showing bilateral interstitial and airspace opacities. **(C)** Computed tomography showing diffuse mosaicism with multiple nodular densities ranging from 3 to 5 mm. **(D)** Computed tomography showing left breast mass with coarse calcifications **(arrow)** and overlying skin thickening.

perfusion scans were negative for deep vein thrombosis and pulmonary embolism, respectively. A CT chest scan showed an enlarged pulmonary artery, mosaicism, and new pulmonary nodules (Figure 3). Despite diuresis and thoracenteses, her hypoxia worsened, requiring mechanical ventilation. TTE revealed severe RV dilation and dysfunction, with Doppler evidence of markedly elevated PVR and LAP. Cytology from thoracentesis was negative for malignancy. She was initiated on sildenafil followed by macitentan, and IV treprostinil was slowly up-titrated. The patient's oxygenation and evidence of airspace disease worsened, and she expired. Based on the severity of her pre-capillary PH in combination with clinical worsening in response to PH therapy, the diagnosis was highly consistent with PVOD.

**CASE 3.** A 47-year-old woman presented with 3 months of increasing dyspnea, fatigue, and unintentional weight loss. On transfer to our institution, she was hypoxic (94% on 5 l/min of supplemental oxygen), was tachycardic, and had a jugular venous pressure of 10 cm of water. A ventilation/perfusion scan raised suspicion for chronic thromboembolic pulmonary hypertension (CTEPH). The patient was suspected to have a pancreatic head mass; endoscopic retrograde cholangiopancreatography biopsy specimens were inconclusive, but her CA 19-9 level was elevated. A CT angiogram showed filling defects in the distal and subsegmental pulmonary circulation without vessel attenuation, atypical for chronic thromboemboli, and suggestive of an intravascular tumor (Figure 4). CTEPH was excluded, and pulmonary tumor obstruction was considered the more likely diagnosis. Subsequent imaging demonstrated a new pleural effusion. Her oxygen requirement gradually increased to 6 l/min. Right heart catheterization revealed severe RV dysfunction, elevated PVR, and normal pulmonary capillary wedge pressure. She was

**FIGURE 4** Case 3

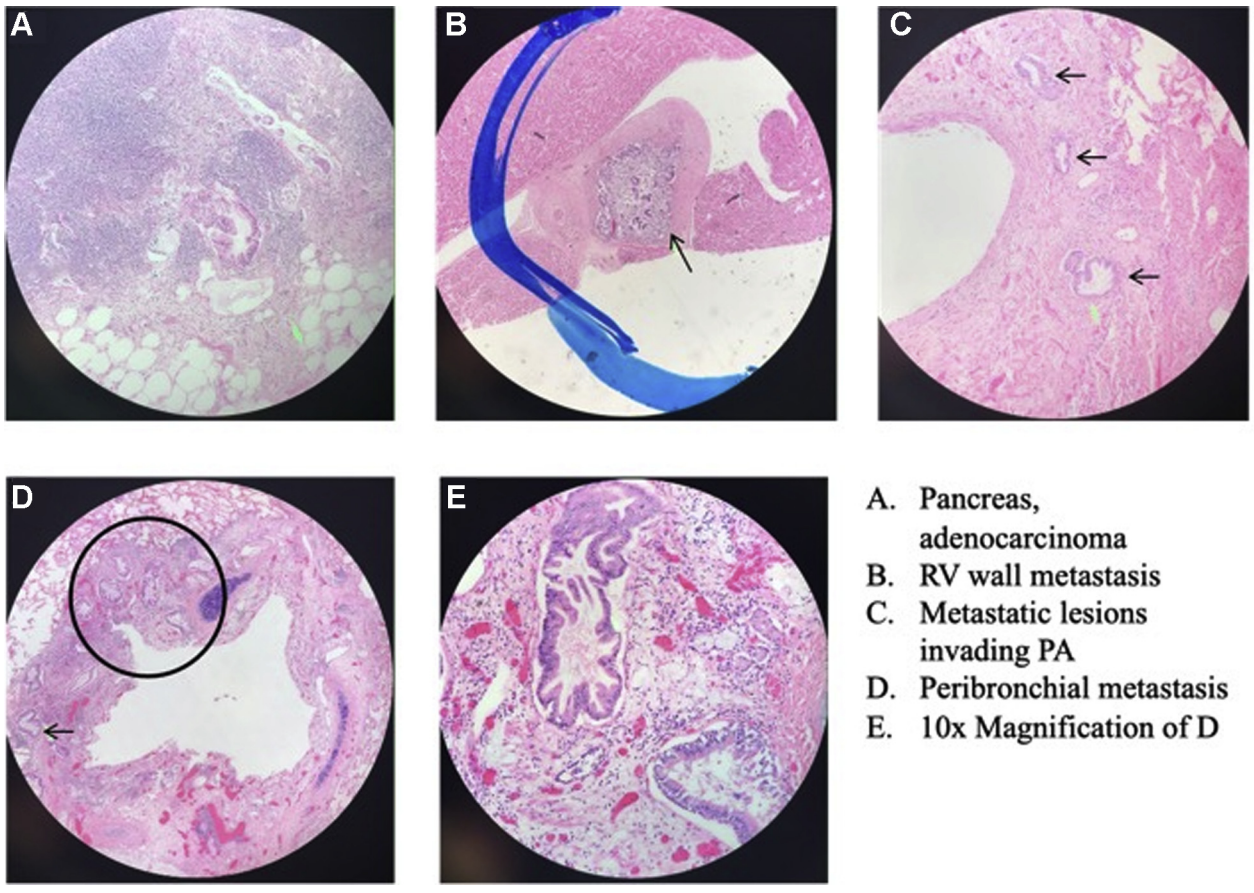



**(A)** Transthoracic echocardiogram showing moderate to severe right ventricular dilation and dysfunction. **(B)** Transthoracic echocardiogram with tricuspid annular plane systolic excursion 1.5 cm and S′ 8 cm/s. **(C)** Computed tomography showing scattered bilateral nodular opacities and interlobular septal thickening **(arrows)**. **(D)** Computed tomography showing eccentric defect without loss of vessel caliber distal to occlusion **(arrows)**. In chronic thromboembolic pulmonary hypertension, as the vessel occludes distally, there is rapid tapering and loss of vessel caliber. In this patient. the vessel volume increases at the site of occlusion, which is highly suggestive of tumor obstruction instead of thrombotic obstruction.

initiated on heparin, riociguat followed by IV treprostinil without improvement. Seven days after starting medical therapy, she began to deteriorate, with worsening dyspnea and rising oxygen requirement. An urgent lung biopsy was scheduled; however, the patient experienced cardiac arrest with pulseless electrical activity and expired. Autopsy confirmed pancreatic duct adenocarcinoma (Figure 5) with widespread metastasis. Evaluation of the lungs was characteristic for lymphangitic carcinomatosa, with numerous malignant mucin glands in the lymphovascular spaces of the bilateral bronchovascular bundle and the RV wall. No special stains were performed to visualize the small pulmonary veins, thus venous obstruction could not be established or excluded. However, given the nature of the overall clinical presentation, the rapid and characteristic decline after starting PH-targeted therapy, and postmortem diagnosis of widespread malignancy involving the pulmonary vasculature, she was determined to have malignancy-associated PVOD.

**CASE 4.** A 77-year-old man presented with 2 months of increasing dyspnea on exertion and chest pain. His medical history included coronary artery disease status post-coronary artery bypass grafting, pulmonary fibrosis, chronic kidney disease, and AF. He was diagnosed with PH 4 months earlier but was not on PH-targeted therapy due to lack of insurance

**FIGURE 5** Case 3 Histology Slides From Autopsy



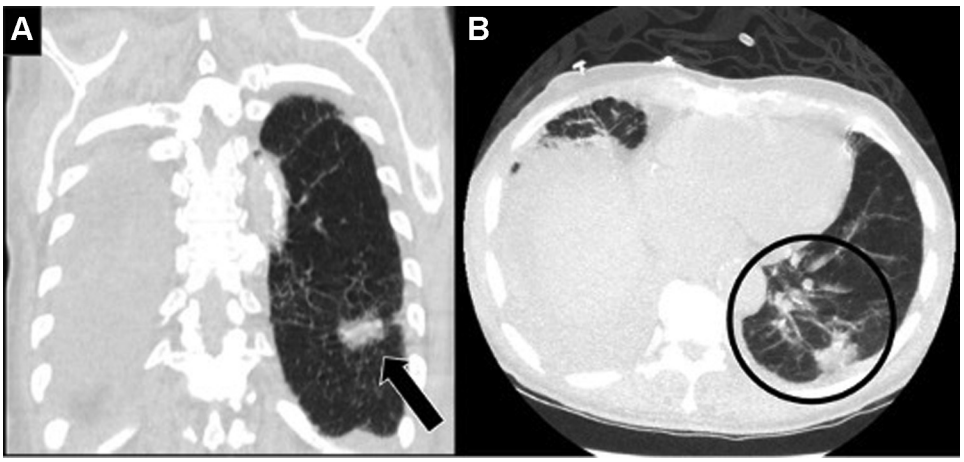

**(A)** Pancreas showing multifocal, mucin-forming, well-differentiated adenocarcinoma in pancreatic body with underlying severe, chronic pancreatitis with destruction of the pancreatic acinar tissue, fibrosis, fat necrosis, and focal hyperplasia of islets. **(B)** Right ventricle with subendocardial vessel with malignant glands **(arrow)** occluding the lumen. **(C)** Pulmonary vasculature showing malignant mucin-producing glands **(arrow)**. **(D and E)** Peribronchial bundle showing vascular congestion, focal hemorrhage **(circle)**, and malignant mucin-producing glands **(arrow, circle)**. PA = pulmonary artery; RV = right ventricular.

approval. TTE and right heart catheterization reports were concerning for PH, severe RV dysfunction, and a low cardiac index. He was initiated on milrinone and transferred to our cardiac care unit. On arrival, his oxygen saturation was 95%. Venous duplex was negative for deep vein thrombosis. A CT chest scan showed fibrosis and interstitial thickening with a new lung mass in the left lower lobe that appeared to be primary bronchogenic carcinoma (Figure 6). Over the next 3 days, he had an increasing oxygen requirement from 5 to 20 l/min. Repeat TTE revealed severe RV dilation and dysfunction, with Doppler evidence of markedly elevated PVR and normal LAP. After starting epoprostenol and sildenafil, the patient became hypotensive and hypoxic, so PH therapy was stopped. The patient rapidly deteriorated and expired due to progression of his severe RV failure. He was thought to have tumor-associated PVOD given his underlying malignancy and acute deterioration after initiation of pulmonary vasodilators.

## DISCUSSION

PH related to tumor obstruction was recently named under Group IV as a non-thromboembolic cause of PH via “other pulmonary artery obstruction” (2). Regardless of classification, these conditions are associated with extremely poor outcomes. Multiple mechanisms have been proposed suggesting the link between cancer and PH: 1) pulmonary vascular endothelial cell injury and apoptosis leading to vasoconstrictive disease (3); 2) thromboembolic disease; 3) tumor emboli; 4) chemotherapy-related causes; 5) vascular remodeling due to inflammatory cell

**FIGURE 6** Case 4




**(A and B)** Computed tomography showing mass-like opacity within the left lower lobe **(A, arrow, B, circle)** measuring 3 cm, likely representative of primary bronchogenic carcinoma (T1B).

accumulation (4); 6) intravascular tumor (i.e., sarcoma); and 7) external malignant compression of the pulmonary artery.

A constellation of findings were consistent in this series:

1. History of a solid tumor (lung, breast, and pancreatic malignancy).
2. Rapid progression of dyspnea and hypoxemia.
3. Severe pre-capillary PH with RV failure, often presenting as a new diagnosis.
4. Severe airspace disease, pulmonary edema, or serious intolerance to PH therapy.

It is highly unusual for a patient with severe and treatment-naive pre-capillary PH to acutely worsen on pulmonary arterial hypertension medical therapy. When this occurs, it is a strong indicator of the presence of post-capillary (often at the venous level) obstruction that is classically PVOD or a PVOD-mimicking process. This is particularly true when the clinical worsening occurs along with an increasing hypoxia and worsening airspace opacity.

## CONCLUSIONS

In the setting of a known malignancy and rapid-onset pre-capillary PH, a PVOD-like process should be suspected. Our case series highlights such a presentation and may assist providers in establishing this unfortunate diagnosis. With a growing cancer population, this is a phenomenon that should be recognized by cardio-oncologists, pulmonologists, and oncologists.

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**KEY WORDS** cancer, malignancy, pulmonary hypertension, pulmonary veno-occlusive disease, PVOD, tumor