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CASE REPORT

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Pulmonary tumor thrombotic microangiopathy: Exploration into current diagnostic aids and therapeutics

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Abstract

Pulmonary tumor thrombotic microangiopathy (PTTM) is an under-recognized cause of pulmonary hypertension and fulminant right ventricle failure. It is associated with a high mortality due to delay in diagnosis. We present two cases of PTTM, both diagnosed postmortem, highlighting the importance of timely identification and initiation of treatment for this near-fatal condition.

KEYWORDS

cancer, metastasis, pulmonary hypertension, right heart catheterization, right ventricle

INTRODUCTION

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare cause of rapidly progressive pulmonary hypertension (PH).[1,2] First reported in 1990 by von Herbay et al.,[2] it remains a fatal disease, with morphological features and precursor lesions observed in nearly 3% of carcinoma patients post-mortem. It involves intimal proliferation, in situ thrombosis, and obliteration of distal resistance pulmonary arterioles.[2,3] In this series, we report two cases of PTTM that led to fulminant right ventricle (RV) failure and death.

CASE 1

A 51-year-old man with past medical history (PMH) of HLA-B27 uveitis and several months of cough, dyspnea on exertion, and bloating presented with rapidly progressive hypoxia, new-onset hypotension, and evidence of end-organ hypoperfusion. Transthoracic echocardiogram (TTE) demonstrated severe dilatation and systolic dysfunction of the RV. Computed tomography (CT) pulmonary angiogram showed no pulmonary embolism (PE) or interlobular septal thickening, but revealed scattered bilateral parenchymal infiltrates with a tree-in-bud appearance, ground glass opacities (GGO), and mediastinal lymphadenopathy.

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PTTM, pulmonary tumor thrombotic microangiopathy; PVOD, pulmonary veno-occlusive disease; VA ECMO, veno-arterial extra corporal membrane oxygenation.

Transbronchial fine needle biopsy revealed no malignancy. As the patient was critically ill, open lung biopsy was not performed. Right heart catheterization (RHC) revealed severe precapillary PH (mean right atrial pressure [RAP]: 17 mm Hg, pulmonary artery pressure [PAP]: 87/42(57) mm Hg, pulmonary capillary wedge pressure [PCWP]: 9 mm Hg, cardiac output (CO): 3 L/min, and pulmonary vascular resistance (PVR): 16.8 wood units [WU]) and no response to acute vasoreactivity testing with inhaled nitric oxide (NO). Work up for associated causes of pulmonary arterial hypertension (PAH) was unremarkable. The patient was initiated on inotropes, endothelin receptor antagonist (ERA), parenteral prostacyclin, and inhaled NO. Due to worsening RV failure, he underwent peripheral veno-arterial extra corporal membrane oxygenation placement; however, he continued to clinically deteriorate and passed away.

Autopsy findings

Evidence of metastatic signet cell adenocarcinoma with tumor micro-emboli in numerous bilateral pulmonary lymphatic spaces, along with intimal and medial thickening of pulmonary arteries and multiple occlusive organized thrombi in intraparenchymal arterioles (Figure 1).

CASE 2

A 44-year-old female with PMH of stage IV metastatic breast cancer ER/PR- HER2+ with new lymphatic metastasis identified on surveillance positron emission tomography presented with 2 weeks of chest pain, shortness of breath, and dry cough. Remarkable initial work-up included serum NT-proBNP of 2650 pg/mL and TTE significant for new-onset RV dilation and dysfunction. A ventilation–perfusion scan showed multifocal peripheral perfusion deficits. CT pulmonary angiogram was negative for acute or chronic PE but revealed increased bilateral GGO. Cardiac magnetic resonance showed severely dilated and dysfunctional RV (Supporting Information: Video 1). RHC revealed precapillary PH (mean RAP 3 mm Hg, PAP 55/30 (38) mm Hg, PCWP 6 mm Hg, CO 3.1 L/min, and PVR 10.3 WU) with no response to acute vasoreactivity testing. Pulmonary wedge aspiration cytology was nondiagnostic. Work-up for associated causes of PAH was negative. The patient received low-intensity intravenous heparin infusion (due to concern for distal chronic thromboembolic PH [CTEPH] based on the abnormal V/Q scan), sildenafil, herceptin, and pertuzumab. After a precipitous decline in oxygen saturation and hemodynamics, the patient passed away.

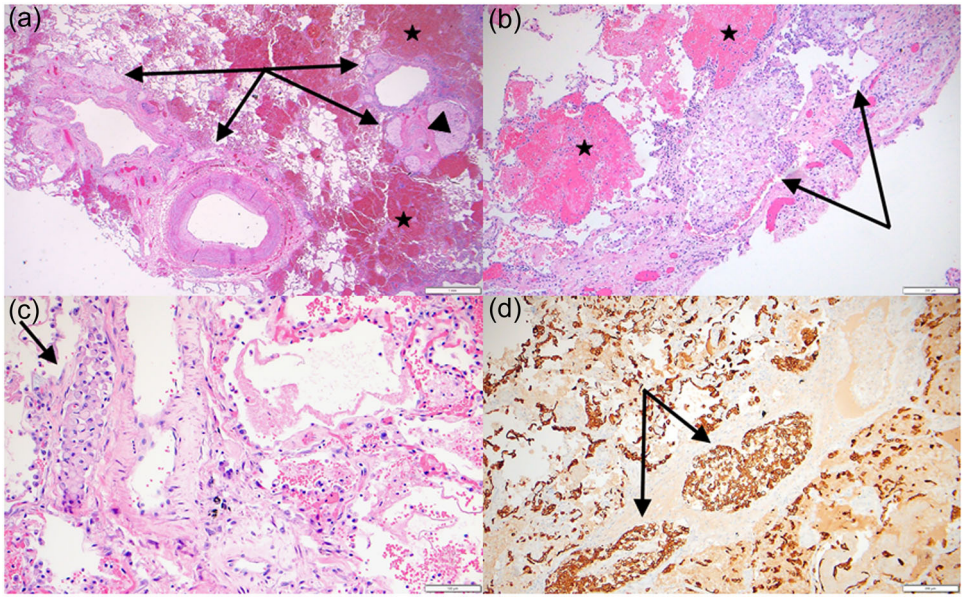

FIGURE 1 Numerous foci of relatively bland, monotonous cells with large central mucin droplets and eccentric nuclei are seen invading lymphatic spaces and small pulmonary vessels (black arrows). The tumor cells are predominantly found within perivascular lymphatic spaces (a, hematoxylin and eosin [H&E], ×20). However, tumor emboli are also seen occluding small pulmonary vessels (b, H&E, ×100; C, H&E, ×200) and pankeratin immunostaining highlights multiple tumor emboli within pulmonary vessels (D, AE1/AE3, ×100). Tumor metastases are often associated with organizing thromboses within numerous pulmonary vessels (black arrowhead), although individual tumor cells within these thrombi are difficult to discern. Foci of tumor are also often seen in conjunction with areas of infarction and hemorrhage (black stars), as well as hyaline membrane formation/diffuse alveolar damage (best appreciated within the alveolar spaces on the right in c).

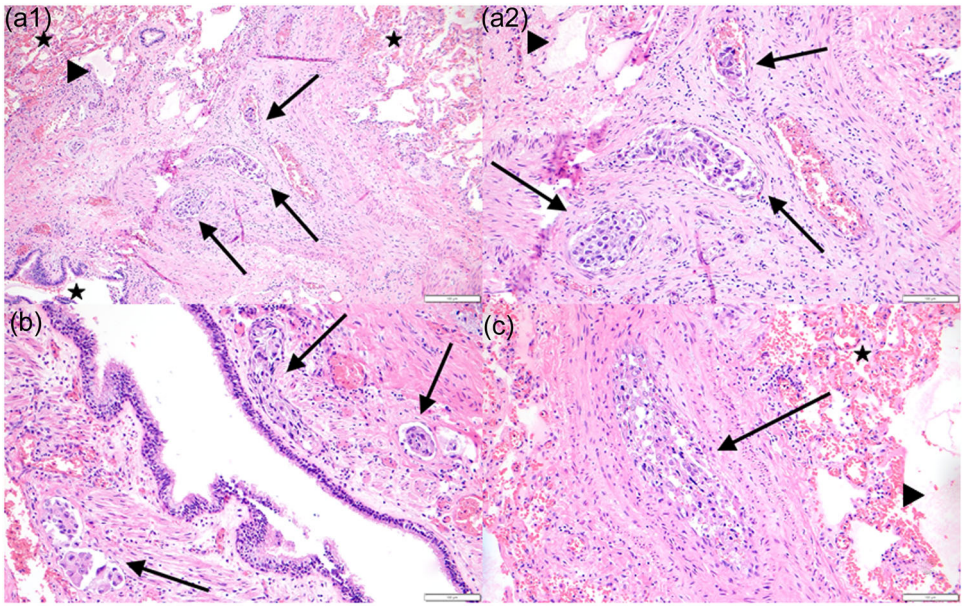

FIGURE 2 Postmortem pneumonectomy specimens demonstrating numerous tumor emboli within the pulmonary vasculature (black arrows). Foci of pleomorphic, cohesive cells with large irregular nuclei and conspicuous nucleoli are seen infiltrating and occluding larger blood vessels (a1, hematoxylin and eosin [H&E], ×100; a2, ×200 magnification of tumor emboli in a1; and (c), H&E, ×200) and small pulmonary vessels, including those within peribronchovascular lymphatic spaces (b, H&E, ×200). Also seen within the lung parenchyma are areas of pulmonary edema (black arrowheads) as well as hemorrhage within the alveoli and airways (black stars).

Autopsy findings

Diffuse metastatic breast carcinoma with alveolar hemorrhage, pulmonary infarction, and abscess formation. Multiple small and large pulmonary vessels had tumor emboli, with some vessels completely obstructed by tumor (Figure 2).

DISCUSSION

Our case series highlights the assident presentation and rapidity in progression of PTTM making antemortem diagnosis a challenge. Circulating tumor cells trigger release of platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) by macrophages. This leads to, neointimal proliferation of distal resistance arterioles\ and development of severe PH.[2,3] The clinical presentation of PTTM includes rapidly progressive dyspnea, cough, and symptoms of right heart failure. Work-up reveals hypoxemia, PH, and RV dysfunction.[1,2] Gastric adenocarcinoma is the causative malignancy in over 50% of PTTM cases, followed distantly by other cancers.[1]

Antemortem diagnostic aids

Abnormal laboratory markers include anemia, elevated plasma D-dimer, high serum lactate dehydrogenase and high serum VEGF levels.[2,4] Radiographic findings include CT evidence of interlobular septal thickening, GGO or tree-in-bud opacities, nodules and mediastinal lymphadenopathy.[1,3] Ventilation perfusion scintigraphy may reveal peripheral perfusion defects secondary to tumor thromboembolism.[5] Pulmonary wedge aspiration cytology and CT-guided transbronchial lung biopsy additionally aid in antemortem diagnosis of PTTM.[6]

Mimics of PTTM

CTEPH, pulmonary veno-occlusive disease (PVOD), and pulmonary capillary hemangiomatosis (PCH) closely mimic PTTM. Key differences lie in the pathophysiology of the disease, chronicity of symptom progression, CT findings, and response to vasodilator therapy.[7] Distinguishing features of PTTM in comparison to CTEPH and PVOD/PCH are detailed in Table 1. Retrospectively, there were clues, especially in our first patient, raising a concern for

TABLE 1 Comparison of key clinical and radiographic findings among patients with PTTM, CTEPH, and PVOD.

Characteristic	PTTM	CTEPH	PVOD
Pathophysiology	Obliterative intimal proliferation of pulmonary arterioles secondary to embolization of tumor cells	Obstruction of medium–large-sized pulmonary arteries due to embolism of organized thrombi	Diffuse obliteration of pulmonary venules by fibrous intimal thickening and capillary proliferation
Symptoms	Acute to subacute dyspnea, cough, symptoms of underlying malignancy	Chronic dyspnea, history of pulmonary embolism, hemoptysis, atypical chest pain	Chronic dyspnea on exertion
Chronology of right heart failure	Acute, rapidly progressive PH and RV failure	Chronic RV dysfunction	Chronic RV dysfunction
Laboratory abnormalities	Anemia, high LDH, elevated D-dimer, high serum VEGF	±Chronically elevated NT pro-BNP	±Chronically elevated NT pro-BNP
CT findings	GGO or tree-in-bud opacities, interlobular septal thickening, nodules and mediastinal lymphadenopath	Pulmonary infarction, mosaic attenuation, GGO, and evidence of chronic thromboembolism	Mosaic attenuation, centrilobular GGO, interlobular septal thickening mediastinal lymphadenopathy, and pleural effusion
V/Q scan	±small mismatched peripheral perfusion defects	Large, mismatched perfusion defects	Normal
Right heart catheterization	Precapillary PH Mean PAP elevated PVR elevated PCWP Normal (<15 mm Hg)	Precapillary PH Mean PAP Chronically elevated PVR Chronically elevated PCWP Normal (<15 mm Hg)	Precapillary PH Mean PAP Chronically Elevated PVR Chronically Elevated PCWP Normal (<15 mm Hg)
Additional diagnostic aids/clues	Pulmonary wedge aspiration cytology; CT guided transbronchial lung biopsy	Invasive pulmonary angiogram and dual energy CT pulmonary angiogram	New-onset pulmonary edema after initiation of vasodilator therapy

Abbreviations: CTEPH, chronic thromboembolic PH; CT, computerized tomography; GGO, ground glass opacities; LDH, lactate dehydrogenase; NT-proBNP, N terminal pro brain natriuretic peptide; PAP, pulmonary artery pressure; PCH, pulmonary capillary hemangiomatosis; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PTTM, pulmonary tumor thrombotic microangiopathy; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RV, right ventricle; VEGF, vascular endothelial growth factor; V/Q, ventilation–perfusion scan.

PTTM. Cough is a very rare manifestation of PAH. In addition, the tree-in-bud appearance on CT chest is more frequently associated with metastatic carcinoma of the lung than PAH, CTEPH, or PVOD/PCH.

Therapeutics

The median survival of patients with PTTM varies from 1 to 15 months after symptom onset, likely affected to a large extent by the clinical index of suspicion.[1] In addition to the treatment of underlying malignancy, systemic anticoagulation, pulmonary vasodilator therapy including phosphodiesterase inhibitors, ERA's and prostacyclin analogs, anti-inflammatory and antiproliferative approaches are reported to slow the progression of PTTM.[1,3,6,8] Tyrosine-kinase inhibitor, imatinib, improves pulmonary hemodynamics by PDGF-receptor blockade and inhibition of downstream signaling pathways.[3,8] Bevacizumab, a VEGF-receptor inhibitor, improves outcomes due to additive block in VEGF expression.[6] Given the pathophysiological role of procoagulant inflammatory pathways, treatment with systemic anti-coagulation is often initiated on presentation.[3,9] Case reports of patients treated with combination of chemotherapy, long-term anticoagulation, and oxygen therapy has shown modest increase in survival.[9] Further exploration to assess the risk-benefit profile of inhibition of growth factors implicated in the proliferative and inflammatory cascade of PTTM is warranted to strengthen the therapeutic possibilities.

CONCLUSION

High index of clinical suspicion, especially among patients with history of carcinoma, is essential for antemortem diagnosis and treatment of PTTM. The diagnosis is often delayed as its clinical and radiographic findings overlap with alternative causes of PH including CTEPH, PVOD, and PCH. The safety and efficacy of pulmonary vasodilator therapies is unclear. Further research into the expansion of diagnostic aids and therapeutics is warranted to improve survival of patients with PTTM.

AUTHOR CONTRIBUTIONS

Pavithra Ramakrishnan and Garima Dahiya worked towards the case review and drafting of the manuscript. Meghan Lindstrom worked on obtaining and critically defining the pathological images obtained postmortem. Thenappan Thenappan worked on revising the manuscript for important intellectual content and for final approval of the manuscript submitted.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. Institutional IRB approval not required in this instance due to the retrospective nature of series encompassing only two clinical cases.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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