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Case report

A case of severe cancer-related pulmonary hypertension; An unexpected resolution

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ABSTRACT

Pulmonary hypertension (PH) in cancer patients can be caused by several mechanisms. It can be a direct cancer effect through pulmonary tumor thrombotic microangiopathy, pulmonary tumor emboli, extrinsic compression, intravascular tumors, or a secondary consequence of therapy, including chemotherapy agents, radiation, and stem cell transplantation. We present the first case of complete resolution of cancer-related PH.

1. Introduction

Pulmonary Hypertension (PH) is a debilitating illness that significantly impacts quality of life and often confers a poor prognosis [1, 2]. It is a known complication of malignancy, and can occur via complex pathophysiological mechanisms, either through direct effects of tumorous microemboli or secondary to cancer-related therapy, including chemotherapy, radiation (RT), and hematopoietic stem cell transplantation (HSCT) [3,4]. When PH occurs in the cancer setting, the mechanisms involved have been traditionally believed to result in permanent effects on the pulmonary vasculature. Therefore, even with treatment, it rarely resolves, and patients often are treatment dependent. We present a case of cancer-mediated PH with complete resolution.

2. Case presentation

A 20-year-old male with a history of recurrent primary mediastinal large B-cell lymphoma (PMLBCL) presented to his hematologist office for a routine visit. He reported progressively worsening exertional dyspnea and palpitations over the course of 10 days. PMLBCL was diagnosed 1.5 years earlier after respiratory symptoms prompted thoracoscopic biopsy. He received 6 cycles of dose-adjusted EPOCH-R chemotherapy (etoposide, prednisone, Oncovin(vincristine), cyclophosphamide, hydroxy-doxorubicin and rituximab). His only lasting adverse effect from the chemotherapy was peripheral neuropathy. The respiratory symptoms markedly improved after therapy. Unfortunately, active imaging surveillance detected local recurrence of disease, which lead to further therapy. He received two infusions of brentuximab, followed by two cycles of ICE chemotherapy (ifosfamide, carboplatin, etoposide and mesna). He then underwent autologous HSCT after high dose bone marrow ablative chemotherapy. Although hospital course was complicated with febrile neutropenia and kidney injury, he did not complain of shortness of breath at the time. After HSCT was completed, he started 2 weeks of radiotherapy (RT) to the thoracic mediastinal mass.

During the second week of RT, he was found to be in mild respiratory distress. Besides dyspnea and palpitations, he denied fevers,

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chills, fatigue, weight loss, chest pain, leg pain or swelling. All symptoms were exertional in nature. Besides sinus tachycardia (heart rate 117/min), cardiopulmonary and other physical examination were normal, and he was hemodynamically stable. Chest radiography was only notable for abnormalities related to his known malignancy. Echocardiography was completed which showed severe PH and signs of right ventricular (RV) failure, including McConnell's sign and hypokinetic RV wall (Fig. 1). Computed tomography (CT) angiography did not reveal any pulmonary arterial emboli but was significant for main pulmonary arterial diameter of 3.5 cm and revealed interventricular septal bowing to the left ventricular (LV) chamber (Fig. 2). He was admitted to the intensive care unit, where right heart catheterization was performed, confirming the echocardiographic findings of severe PH (Table 1). The mean pulmonary arterial pressure was 43 mmHg and pulmonary capillary wedge pressure was 6 mmHg. A ventilation perfusion scan was performed to evaluate for chronic thromboembolic disease, which was unremarkable. High-resolution CT of the chest 3 days after the initial study revealed patchy parenchymal ground glass opacities. Treatment with Treprostinil lead to remarkable symptomatic improvement. Steroids were also given due to concerns that radiation-induced pneumonitis may have at least partially contributed to symptoms. Patient was then discharged with subcutaneous treprostinil therapy and a prednisone taper.

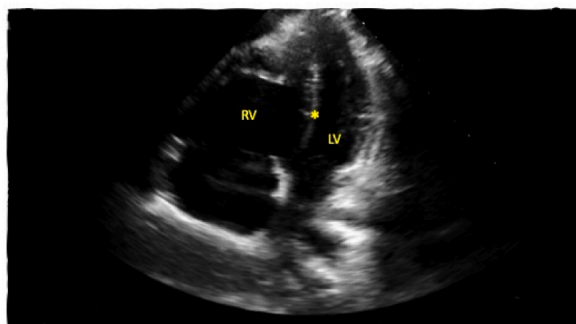
He was seen in the clinic 3 weeks after discharge, with repeat echocardiogram showing near normalization of the RV pressures. Given remarkable response to therapy, he was transitioned to oral tadalafil and ambrisentan. He reported virtually no symptoms and was able to perform intense cardiovascular exercise without issues. Repeat echocardiograms over the next 1.5 years showed persistent normal RV pressure and function, and he was completely weaned off therapy. A final echocardiogram following discontinuation of all therapy confirmed previous normal findings (Fig. 3). Furthermore, several PET-CT scans over the same period consistently confirmed resolution of malignancy. Fig. 4 summarizes the previously narrated timeline.

3. Discussion

We present a peculiar case of complete resolution of cancer-related severe PH. To our knowledge, there are no such cases reported in the literature. We only found one case where PH quickly responded to steroid therapy [5]. However, there was no long-term follow up or objective evidence of complete resolution. There are two important questions to answer in this case. The first is the etiology of PH. There are several possibilities, given his cancer history, exposure to multiple chemotherapeutic drugs, stem cell transplantation and radiotherapy. On a similar note, it is very possible that PH was multifactorial for that reason. PH related to hematological disorders is a well-known subtype of Group 5 PH [1,2]. Group 5 PH is a heterogeneous entity that includes multiple etiologies. The acute presentation soon after initiation of RT suggests this to be at least a contributor. Another potential culprit is HSCT, which was completed only one month prior to his presentation. Both RT and HSCT can cause pulmonary veno-occlusive disease (PVOD), a phenotype of group I PH that is characterized by a progressive narrowing of the pulmonary veins and subsequent remodeling [3]. Furthermore, it is possible that the patient had a certain degree of asymptomatic PVOD that was previously induced by chemotherapy. This may be especially true since review of an echocardiogram before PH was diagnosed, but after chemotherapy, revealed mildly elevated RV pressures (Fig. 3). Definite association between specific chemotherapeutic agents and PVOD has been difficult to prove since most patients usually receive regimens containing multiple agents. However, evidence strongly suggests both vincristine and cyclophosphamide (both of which patient received) to cause PVOD [6].

Malignancy can also cause PH through pulmonary tumor thrombotic microangiopathy (PTTM). This entity is thought to be induced by tumor microemboli causing activation of the coagulation cascade and endothelial proliferation in the pulmonary vasculature, again resulting in remodeling and PH [7,8]. The acuity of the presentation after RT and lack of residual disease in this case argues against PTTM being the cause. Finally, Intravascular large B-cell lymphoma (IVLBCL) is an extranodal form of lymphoma limited to the blood vessels. This is a very rare cause of PH [3]. However, review of the pathology report from diagnosis reveals that the mediastinal mass was invading the lung, and it is possible that tumor cells were invading the pulmonary capillaries, but again the lack of residual disease means this is highly unlikely.

The second and equally important question is why PH completely resolved. All the mechanisms of PH in cancer patients known to date involve permanent changes in the pulmonary vasculature. This is especially true for PVOD, which is virtually always fatal and only lung transplantation provides sustained therapy. It is possible that this patient presented in the early stages of the remodeling



PH pulmonary hypertension; RV right ventricle; LV left ventricle; * bowing of the interventricular septum

Fig. 1. Echocardiogram at time of presentation with PH.

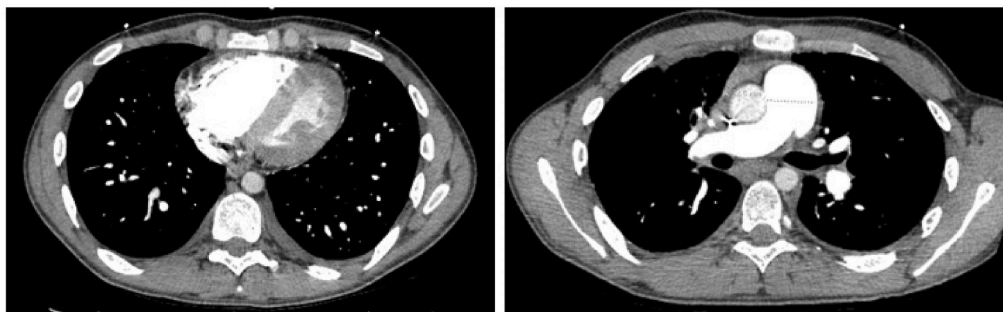
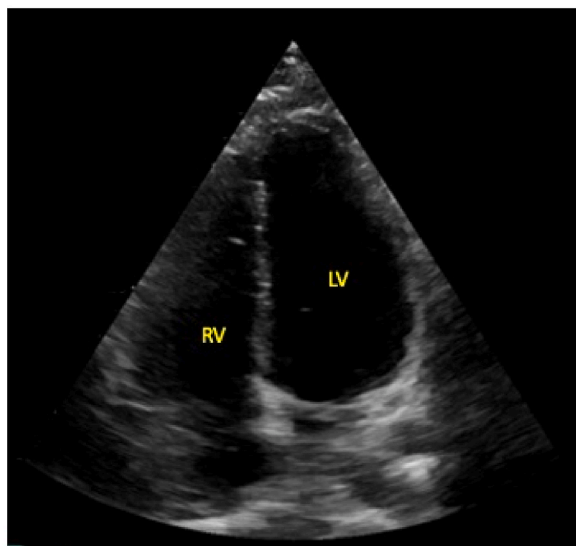


Fig. 2. Chest computed tomography angiography.

Table 1
Right Heart Catheterization data.

Before NO administration	
PAP	65/30 mmHg
MPAP	43 mmHg
PVR	722 dyn/sec/cm ⁻⁵
PCWP	6 mmHg
CI	L/min/m ²
10 minutes after NO administration	
PAP	40/18 mmHg
MPAP	25 mmHg

NO nitric oxide; PAP pulmonary arterial pressure; MPAP mean pulmonary arterial pressure; PVR pulmonary vascular resistance; CI cardiac index.



PH pulmonary hypertension; RV right ventricle; LV left ventricle

Fig. 3. Echocardiogram 20 months after diagnosis of PH.

process and that the aggressive steroid and prostacyclin therapy suppressed the inflammatory and proliferative cascade early. The pathophysiological mechanisms causing PH in cancer are intricate and poorly understood. Studying these mechanisms require molecular and pathological analysis that is rarely available in sufficient number of subjects to generate statistically significant data. An unknown mechanism may potentially provide an explanation for the resolution of PH in our case.

4. Conclusion

- We present an unusual case of resolved cancer-related PH.

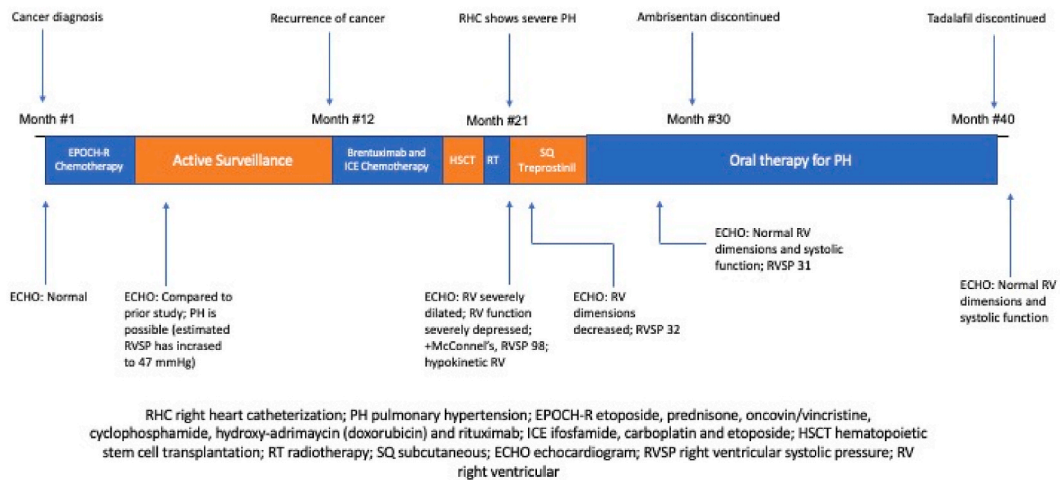


Fig. 4. Timeline.

- The pathophysiological mechanisms of PH in cancer patients are complex and poorly understood.
- Further studies on the mechanisms of PH may shed light on the reason behind complete recovery in some incidental cases.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Declaration of competing interest

None of the authors have any conflict of interest.

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