CASE STUDY

Pulmonary Artery Intimal Sarcoma and the Role for Vasodilator Therapy—A Case Report and Scoping Review

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Pulmonary artery sarcoma is a rare disease that is often misdiagnosed as acute or chronic pulmonary thromboembolism due to its clinical presentation and radiological findings. Often, right ventricular failure is observed due to pulmonary hypertension caused by the obstructive effect of the tumor and concomitant chronic thromboembolism. In this article, we report a rare case of a 60-year-old male patient presenting with dyspnea and imaging findings suggestive of a pulmonary embolism. He was treated with standard anticoagulation and thrombolytic therapy yet continued to have symptoms, with repeat imaging showing progression of disease. The patient subsequently underwent surgical resection of the obstructive lesion, with pathology revealing sarcoma. On follow-up clinic visits, our patient continued to endorse shortness of breath with evidence of pulmonary hypertension. Pulmonary artery sarcoma has been mainly documented through case reports, and treatment often centers around surgical resection and oncological intervention. Many of these patients often have right-sided heart failure. The goal of this review is to systematically search through the literature, identify vasodilatory therapies that have been used in patients with pulmonary artery intimal sarcoma, and characterize the role of pulmonary hypertensive medications.

INTRODUCTION

Pulmonary artery sarcoma (PAS) is an uncommon, but increasingly recognized, thoracic malignancy with only a few hundred cases reported in the literature.[1] The sarcoma arises from mesenchymal cells of the intimal layers of the pulmonary trunk and artery. It has a slight female predominance with no other associated risk factors currently known.[2] PAS results in significant morbidity and high mortality, with a median survival of just 1.5 months.[3] Typically, the disease presents in adulthood, with symptoms including dyspnea, cough, hemoptysis, chest pain, and weight loss. The clinical and radiological findings are often similar to those of thromboembolic disease, leading to delays in confirming the diagnosis. Due to the overall clinical picture of thromboembolic disease, the majority of these patients are diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH).[4]

Given the rarity of PAS, only case reports and small case series have been published, the majority focusing on histopathological appearances and surgical aspects of its management. Surgery remains the mainstay of management for patients with PAS.[5] The role of additional chemotherapy and radiotherapy after surgical resection remains largely unproven. We present a case of a 60-year-old male presenting with dyspnea, with imaging demonstrating occlusion of the right pulmonary artery found to have PAS.

Additionally, we systematically searched through the literature to identify vasodilatory therapies that have been used in patients with pulmonary intimal sarcoma to characterize the role that pulmonary hypertensive medications may play.

ETHICS STATEMENT

The patient identified in this case study has provided written consent for the publication of their medical case, with the understanding that anonymized information will be shared for educational and research purposes. Given the nature of the case study, which does not involve any experimental procedures or interventions beyond standard medical care, institutional review board approval was not deemed necessary.

CASE

A 60-year-old male patient with a past medical history of transient ischemic attacks on lifelong anticoagulation with rivaroxaban, hypertension, and type 2 diabetes mellitus presented to his primary care doctor with complaints of 5 days of dyspnea. Vital signs demonstrated a heart rate of 106 beats per minute, blood pressure of 138/80 mm Hg, respiratory rate of 18 breaths per minute, and oxygen saturation of 95% on ambient air that remained above 90% with ambulation. Physical exam revealed nonlabored breathing with lungs that were clear to auscultation bilaterally. Electrocardiogram showed sinus tachycardia. A posteroanterior and lateral chest

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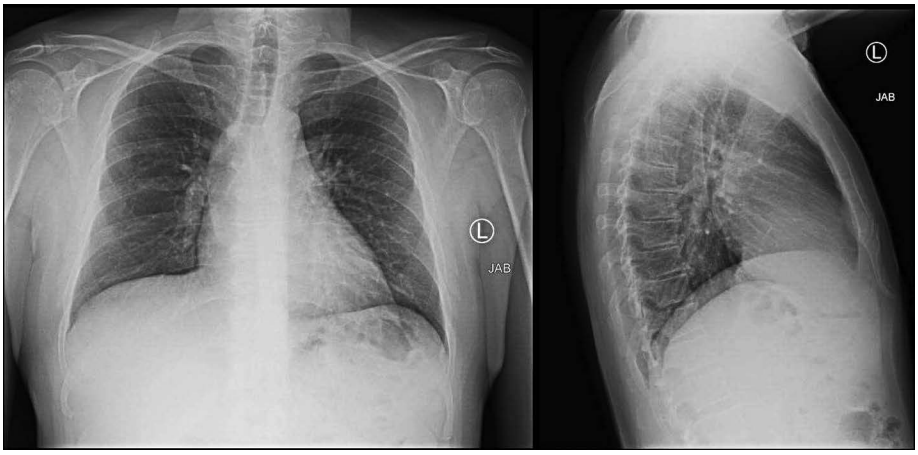

Figure 1: A posteroanterior and lateral chest x-ray obtained on patient initial presentation.

radiograph was unremarkable without any pulmonary infiltrates or consolidations (Figure 1). As he was already on rivaroxaban, the likelihood of pulmonary embolism was thought to be low. He was prescribed azithromycin and prednisone for presumed community-acquired pneumonia with close follow-up.

One week later, the patient continued to have persistent dyspnea despite treatment. Coronavirus disease 2019 and influenza testing were negative. The physical exam was otherwise unchanged from his previous visit. Due to his persistent symptoms with unclear etiology, he was sent to the emergency department for further evaluation. Serological testing, including complete blood count, basic metabolic panel, and liver function tests, were unremarkable. High-sensitivity troponin-T was elevated at 30 ng/L. Electrocardiogram again demonstrated sinus tachycardia.

A computed tomography (CT) pulmonary angiogram revealed an extensive right-sided pulmonary embolism extending from the bifurcation of the central pulmonary artery without extension of thrombosis in segmental and subsegmental vessels as well as the left pulmonary artery and lobe (Figure 2). Emergent echocardiogram showed an ejection fraction of 55% with severe enlargement of the right ventricular chamber and reduced systolic function. The estimated right ventricular systolic pressure was 69 mm Hg, with a peak tricuspid regurgitation velocity of 3.1 m/s. He was initiated on unfractionated heparin infusion for intermediate- to high-risk pulmonary embolism and underwent evaluation for thrombectomy with interventional radiology. Initial diagnostic pulmonary angiogram demonstrated patency of the main left pulmonary artery with preserved perfusion of the left lung. However, there was complete absence of flow of contrast within the main right pulmonary artery correlating to the complete thrombosis of the vessel. Due to the suspected extensive thrombus burden within the vessel, there was difficulty achieving the most adequate position of the guide sheath and catheter within the main right pulmonary artery for thrombectomy. Instead, catheter-directed thrombolysis was performed, with the infusion catheter being placed along the course of the main right pulmonary artery for maximal thrombolytic therapy.

During his hospitalization, he became hypoxic and required supplemental oxygen. An ultrasound of his bilateral lower extremities did not show any deep vein thrombosis, so interior vena cava filter was deferred. On hospitalization day 5, the patient had sudden acute chest pain with a heart rate of 83 beats per minute, blood pressure of 125/67 mm Hg, and oxygen saturation of 91% on 2 L nasal cannula. Repeated serologies again were unremarkable outside of a recurrent elevated high-sensitivity troponin at 39 ng/L. A repeat CT pulmonary angiogram was conducted that demonstrated progressive thrombosis with extension throughout the right main pulmonary artery, right lobar, segmental, and subsegmental arteries. New findings of left-sided segmental and subsegmental emboli along with a tiny embolus within the left main pulmonary artery were also revealed. Repeat thrombolysis was considered, but given the progression and extensive clot burden, this was deferred for evaluation of mechanical thrombectomy by cardiothoracic surgery. His clinical condition improved, with resolution of his chest pain and hypoxic respiratory failure as he returned to ambient air.

The patient was transferred to the university medical center 9 days after initial hospitalization for cardiothoracic surgery evaluation. Repeat CT pulmonary angiogram again demonstrated unresolved

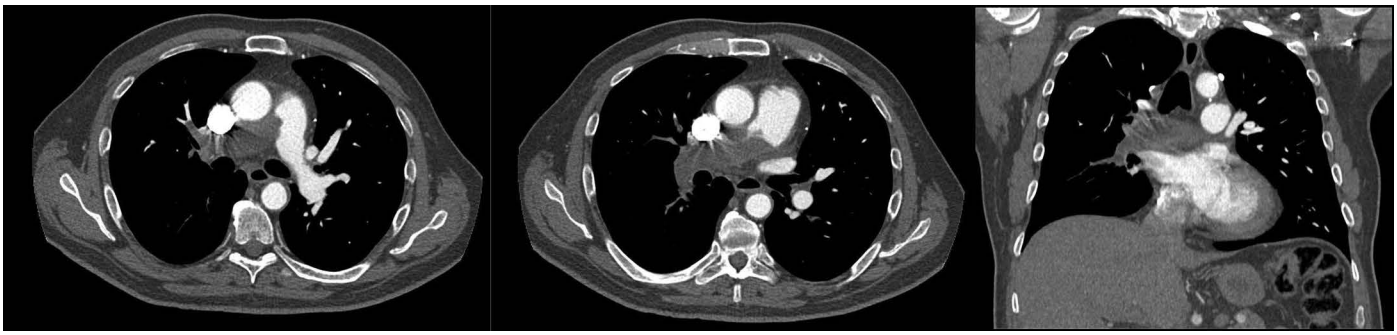

Figure 2: Computed tomography pulmonary angiogram revealing right-sided occlusion lesion extending from the bifurcation of the central pulmonary artery into the left pulmonary artery and lobe.

thrombi that were unchanged from his prior scan. He underwent right and left heart catheterization that revealed a completely occluded right main pulmonary artery ostium, patent left main pulmonary artery main vessel, and triple-vessel disease, including mid-left anterior descending, mid-right coronary artery, and first obtuse marginal. Pulmonary artery pressure was elevated at 86 mm Hg, and pulmonary capillary wedge pressure was normal at 7 mm Hg. He underwent bilateral pulmonary endarterectomy and 3-vessel coronary artery bypass grafting 12 days into admission. Gross surgical specimens from the endarterectomy were sent for pathology evaluation. Postoperatively, he was transferred to the cardiac intensive care unit for monitoring, where he was initiated on intravenous milrinone and inhaled nitric oxide. His stay was complicated by acute renal failure from acute tubular necrosis that required short-term hemodialysis with eventual renal recovery. He was discharged 16 days after initial hospitalization presentation with warfarin for anticoagulation, furosemide for diuresis, sildenafil for pulmonary hypertension, and 2 L of supplemental oxygen.

One day after hospitalization, the pathology review of the specimens from the endarterectomy revealed the diagnosis of intimal sarcoma. The patient was established with oncology follow-up 1 week after hospitalization, and he underwent positron emission tomography-CT, with multiple bone lesions consistent with osseous metastasis. He was readmitted to the hospital with initiation of doxorubicin, ifosfamide, and mesna chemotherapy. He completed 6 cycles of chemotherapy with repeat positron emission tomography-CT, demonstrating resolution of his disease. He was considered to be in remission of his malignancy.

He followed up with the pulmonology clinic for his pulmonary hypertension that was still being treated with sildenafil around 6 months after initial discharge. He was World Health Organization functional class III with progressive dyspnea but no longer required supplemental oxygen. Pulmonary function testing demonstrated severe diffusion limitation, with diffusion capacity of carbon monoxide of 38% of predicted. Repeat echocardiogram demonstrated an improved ejection fraction of 65%, with improvement of right ventricular systolic function to normal and minimal tricuspid regurgitation jet with inability to calculate right ventricular systolic pressure. The patient was scheduled for repeat right heart cauterization with vasoreactivity testing to determine potential palliative trial of oral vasodilator therapy for his severe dyspnea.

Less than 1 week later, the patient had new-onset left-sided leg and foot weakness and underwent magnetic resonance imaging of his brain and lumbar spine that revealed osseous metastatic disease with multiple lesions within the brain. A biopsy of a lesion on his lumbar spine was performed but was unable to be identified due to complete necrosis of the tissue. Due to overall concern of recurrent metastatic intimal sarcoma, he was started on palliative radiotherapy for his brain metastasis.

Before initiation of radiotherapy, he presented to an outside emergency department after having seizure-like activity and was found to have worsening vasogenic edema on a CT head scan. He was hospitalized and had multiple complications, including atrial fibrillation with rapid ventricular response, acute renal failure, and *Clostridioides difficile* colitis. He progressively went into septic shock, requiring an upgrade to the intensive care unit and norepinephrine and intubation. Unfortunately, the poor prognosis of the patient's condition was discussed with the family, who decided to transition to comfort-only care. He expired after cessation of aggressive life support measures.

METHODS AND MATERIALS

The goal of this scoping review was to conduct a systematic search of the existing literature and to characterize the evidence supporting vasodilatory treatment regimens for PAS-associated pulmonary hypertension. The methodology for this scoping review was based on the protocol outlined by Arksey and O'Malley.[6]

The literature search, scope, and reporting of findings were guided by the following questions:

1. What treatments have been used to address pulmonary hypertension in patients with PAS?
2. What is the role of vasodilator therapy in patients with PAS with right heart failure?
3. Are there potential avenues for future research?

Search Strategy

The initial literature search was completed by our team librarians using the search terms "pulmonary artery sarcoma," "pulmonary hypertension," "vasodilator," "therapy," "right ventricular failure," "afterload reduction," "riociguat," "pulmonary artery balloon angioplasty," and "diuresis" on the databases PubMed, Ovid MEDLINE, Embase, Cochrane Library, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, NHS Economic Evaluation Database, and ClinicalTrials.gov.

The date January 1, 1995, was designated the start date for the literature review after a preliminary search on PubMed revealed an increase in "pulmonary artery sarcoma" publications under their "Results by Year" filter. The systematic search was conducted on the publications in electronic databases from January 1, 1995, to September 1, 2022. This neither includes unpublished ongoing studies as of September 1, 2022, nor conferences, newsletters, or book chapters.

All citations (880) were imported into EndNote X8.0.1 (Thomson Reuters). The citations were then deduplicated and uploaded into Covidence (Covidence, Melbourne, Australia), an online tool to help organize and facilitate the literature selection process.

Study Selection

Two team members independently reviewed each title and abstract for the initial screening process. A third member assisted with providing consensus for cases of disagreement. The screening process was iterative. Only articles that included vasodilatory treatment for PAS were included. Studies that partially fulfilled the inclusion criteria, such as those discussing only surgical or oncologic interventions, were not included in this study. Full articles were

obtained, and their references were screened for additional relevant articles.

Charting the Data

The data from primary research articles (studies that generate new data) were compiled in a single spreadsheet. Secondary research articles, such as reviews, were not directly included in the data collection process, but they were consulted to determine additional studies that may not have been included through our screening process. Finally, individual case studies were grouped together and evaluated for common themes.

RESULTS

The total number of papers obtained from the initial database search was 880. After eliminating duplicates, this review began with 502 articles. After reviewing titles, 426 articles were excluded. Excluded articles encompassed a broad range of topics that did not discuss primary PAS. For example, articles that discussed embolic metastases of another malignancy, cardiac sarcomas, vasculitis, or congenital pulmonary artery abnormalities were not included.

In total, 76 articles were screened based on their abstracts. Articles that did not discuss both primary PAS and pulmonary hypertension were excluded, which brought the final count to 23 articles for full-text screening. Only 2 studies addressed the use of pulmonary hypertensive medications in the management of primary pulmonary sarcomas. The 21 excluded articles discussed pulmonary hypertension as a complication of the PAS but did not discuss its medical management outside of surgical resection or oncologic therapies. The preferred reporting items for systematic reviews and meta-analyses flow chart details the review process (Figure 3).

DISCUSSION

PAS is a rare tumor that arises in the central pulmonary arteries. Often, patients present with shortness of breath, with imaging suggestive of a pulmonary embolism. Despite anticoagulation or thrombolysis, lesion excision is usually performed to reveal the malignancy due to persistent symptoms by patients. Prognosis ranges from several months to a few years depending on the extent of disease, the presence of recurrence or metastasis after surgical resection, and the use of adjuvant therapy like radiation and chemotherapy. The evidence supporting the management of PAS is limited to case studies and series, all of which discuss the immediate surgical and oncologic management.

This case experience is unique because it adds to the medical management of PAS by using vasodilator therapy for pulmonary hypertension. The physiology of pulmonary hypertension from a primary malignancy in the pulmonary vasculature is different from that of an embolic process as the increase in pulmonary artery pressure occurs chronically, which allows for right ventricular compensation. The scoping review process has identified multiple case reports documenting the coexistence of pulmonary hypertension in patients with PAS, but only 2 studies discussed the use of vasodilatory therapy in postoperative management. None of these patients were continued on pulmonary hypertension treatment at discharge. Most patients died from within the same hospitalization of diagnosis, so the evidence for vasodilator therapy is minimal.

Interestingly, the scoping review process identified an area of research that involves using vasodilators for symptom palliation in patients with end-stage interstitial lung disease. By targeting the pulmonary blood vessels, sildenafil can help reduce pulmonary hypertension, a common complication of interstitial lung diseases. Bajwah et al[7] conducted a systematic review assessing the level of evidence of interventions aimed at improving dyspnea and other quality-of-life metrics in patients with fibrotic interstitial lung disease and concluded that there is moderate evidence for the use of sildenafil in improving patient's dyspnea and quality of life. Given pulmonary sarcoma's high morbidity and mortality, it is worthwhile to explore

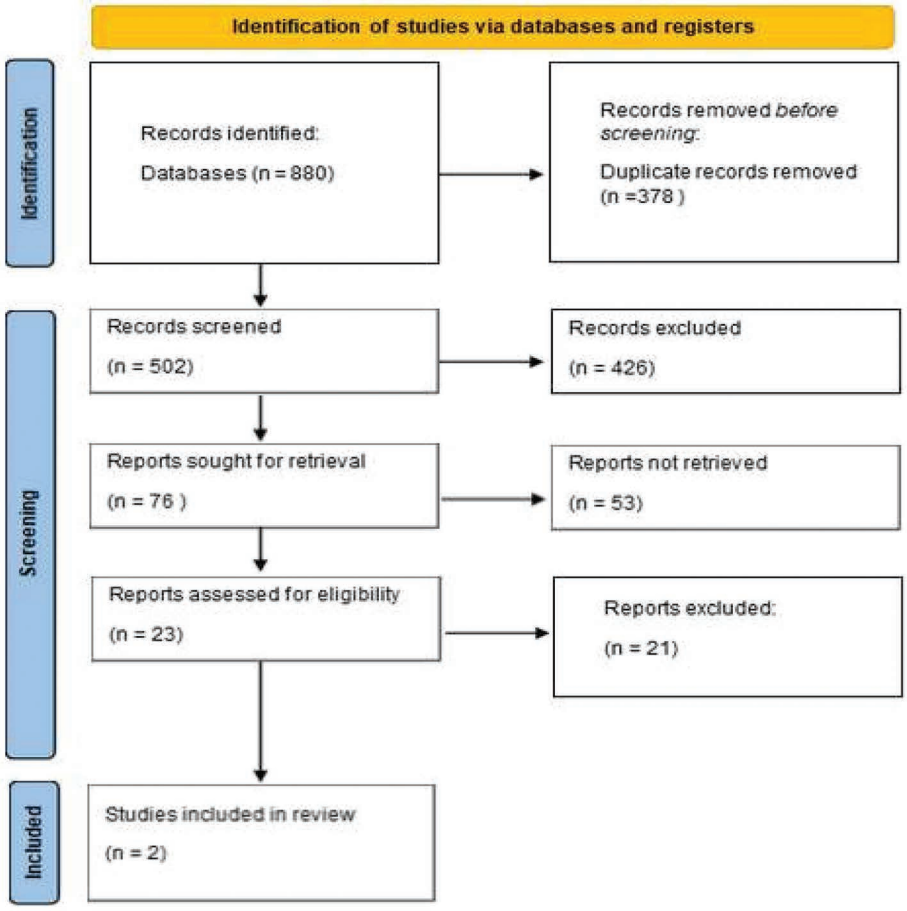

Figure 3: Preferred reporting items for systematic reviews and meta-analyses flow detailing the systematic review process.

future uses of vasodilators for palliative purposes for patients with PAS.

Right ventricular heart failure pathogenesis from PAS is similar to that from CTEPH because both are caused by obstruction preventing perfusion of normal lung parenchyma. Right ventricular failure is the main cause of morbidity and mortality in pulmonary hypertension and CTEPH, so successful treatments should lead to improvements in right ventricular parameters. Thus, there may be a theoretical role for a medication like riociguat, a soluble guanylate cyclase stimulator approved to treat both pulmonary arterial hypertension and nonoperable CTEPH, in symptom palliation in patients with PAS.

Riociguat increases the production of cyclic guanosine monophosphate, leading to relaxation and dilation of blood vessels. In both preclinical and clinical studies, riociguat has demonstrated a beneficial impact on right ventricular structure and function. A range of hemodynamic parameters, including pulmonary vascular resistance, cardiac index, mean pulmonary artery pressure, and systemic vascular resistance, were improved in both pretreated and treatment-naive patients in PATENT-1 and in patients with inoperable CTEPH and persistent/recurrent CTEPH post-pulmonary endarterectomy (PEA) in CHEST-1.[8,9]

Given that riociguat has the ability to reduce pulmonary vascular resistance, there is a basis for considering its use in patients with PAS. By improving blood flow and reducing pressure in the pulmonary arteries, riociguat might help alleviate some of the symptoms associated with the condition, such as shortness of breath and chest pain. This may improve patient quality of life while more definitive therapy such as chemotherapy or surgical resection is being considered.

Currently, riociguat has the most evidence supporting its use in nonoperative CTEPH. However, there are other medications being studied for use in nonoperative CTEPH but have not been approved for use worldwide. Subcutaneous treprostinil showed improvement in right heart hemodynamic measurements (CTREPH trial), and it has been approved for use in Europe.[10] Macitentan is currently undergoing a phase 3 trial (MACiTEPH)[11] after positive results from the MERIT-1 study investigating the efficacy, safety, and tolerability of macitentan.[12] These agents may have potential palliative use in PAS, but their current use is pending additional studies.

This study is limited because it is a discussion of a single patient case. Additionally, the patient was started on pulmonary hypertensive medications for 3 months, but he died 6 months after diagnosis. Follow-up studies evaluating the progression of the patient's pulmonary hypertension were unable to be conducted due to the patient's passing. The prognosis of PAS is poor despite conventional surgical and oncologic therapy. However, this patient case does raise a new clinical question of whether incorporating a vasodilator medication for PAS-associated pulmonary hypertension could improve or prolong a patient's functional capacity and quality of life.

CONCLUSIONS

PASs are a rare thoracic malignancy that can lead to pulmonary hypertension through vascular obstruction. Vasodilatory medications are used to dilate the constricted blood vessels, reduce pulmonary hypertension, and improve blood circulation in the lungs. These therapies can result in alleviation of dyspneic symptoms and potentially improve patient quality of life.

We present a case of PAS in which the patient was started on vasodilatory treatment with the goal of symptom palliation. However, the effectiveness of vasodilatory therapy in PASs have not been studied as noted through a systematic search of the literature. There is moderate evidence supporting the use of vasodilators in end-stage interstitial lung disease for palliative purposes, and this could be applied to patients with PAS.

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