Case Report

Dasatinib-Induced Persistent Pulmonary Arterial Hypertension Treated with Sequential Bosentan and Riociguat Therapy: A Case Report

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Highlights

- Dasatinib-associated pulmonary arterial hypertension may persist despite drug withdrawal and clinical improvement.
- Sequential bosentan and riociguat therapy improved clinical status and hemodynamics in persistent PAH.

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ABSTRACT

Background: Dasatinib is a tyrosine kinase inhibitor commonly used as first-line treatment for chronic myeloid leukemia (CML). Although pulmonary complications are uncommon, dasatinib has been associated with serious adverse effects, including pulmonary arterial hypertension (PAH). Dasatinib-related PAH is currently categorized within group 1 PAH associated with drugs and toxins. We present a case of persistent PAH that developed during long-term dasatinib therapy and was managed with sequential bosentan and riociguat.

Case Presentation: A 52-year-old woman with chronic-phase CML developed progressive exertional dyspnea and fatigue after 5 years of dasatinib treatment. She also had severe PAH and bilateral pleural effusions. Transthoracic echocardiography revealed right-sided cardiac enlargement, with a tricuspid regurgitation jet velocity of 3.9 m/s. Right heart catheterization confirmed precapillary pulmonary hypertension consistent with group 1 PAH. Thoracic computed tomography demonstrated bilateral pleural effusions. Dasatinib-related PAH was considered the most likely diagnosis; dasatinib was discontinued and replaced with nilotinib. Prednisolone was administered for approximately 4 months for the pleural effusion.

According to the 2022 ESC/ERS pulmonary hypertension guidelines, the patient was classified as being at intermediate risk before initiation of PAH-targeted combination therapy. Bosentan was initially prescribed. Because the clinical and hemodynamic response remained inadequate, riociguat was subsequently added. Following the introduction of riociguat, the patient's symptoms improved substantially, and the clinical risk status decreased to the low-risk category. Nevertheless, right heart catheterization performed after 1 year of combination treatment demonstrated persistent pulmonary hypertension despite the marked clinical improvement.

Conclusion: Dasatinib is an important therapeutic option for patients with CML but may cause persistent pulmonary vascular abnormalities. Prompt recognition of PAH, withdrawal of dasatinib, and appropriately individualized PAH-directed treatment may lead to substantial clinical and hemodynamic improvement. This case also highlights the possibility that pulmonary vascular abnormalities may persist despite symptomatic recovery.

Keywords: Dasatinib; Riociguat; Pulmonary Arterial Hypertension (PAH); Tyrosine Kinase Inhibitors; Chronic Myeloid Leukemia (CML)

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Introduction

The introduction of *BCR-ABL* tyrosine kinase inhibitors (TKIs) has substantially improved the prognosis of patients with chronic myeloid leukemia (CML). Dasatinib, a second-generation TKI, is widely used in the management of CML and is an established first-line therapeutic option.

Although generally well tolerated, dasatinib has been associated with several pulmonary adverse effects. Pleural effusion is relatively well recognized, whereas pulmonary hypertension and pulmonary arterial hypertension (PAH) are less frequent but potentially serious complications. Dasatinib-associated PAH is classified as group 1 PAH related to exposure to drugs and toxins.[1,2] With accumulating evidence from case reports, case series, and observational studies, dasatinib-associated PAH was subsequently recognized as a definitive rather than merely possible drug-related cause of PAH at the 6th World Symposium on Pulmonary Hypertension in Nice.[3]

Case Presentation

A 52-year-old woman with chronic-phase CML was admitted to the hospital in March 2019 because of progressively worsening dyspnea and fatigue. Her symptoms had developed over approximately 6 months and had progressed to severe shortness of breath even with minimal physical activity.

The patient had been diagnosed with CML in 2014 and had received dasatinib at a dose of 100 mg once daily for 5 years. She had no previous history of cardiac or pulmonary disease and no other significant comorbidities. At presentation, her blood pressure was 110/70 mm Hg, and her heart rate was 90 beats/min. Physical examination revealed a grade 2/6 systolic murmur along the left sternal border and bilateral peripheral edema. The electrocardiogram did not demonstrate any specific abnormality.

Transthoracic echocardiography showed normal left ventricular and left atrial dimensions, with preserved left ventricular systolic function and an ejection fraction of 65%. In contrast, the right-sided cardiac chambers were enlarged. The basal right ventricular diameter was 46 mm, while the right atrial area was 18 cm² (Figure 1). The tricuspid regurgitation jet velocity was 3.9 m/s, and tricuspid annular plane systolic excursion (TAPSE) was 19 mm. Based on the New York Heart Association (NYHA) classification, the patient was in functional class III.

Right heart catheterization demonstrated a pulmonary artery systolic pressure of 60 mm Hg, pulmonary artery diastolic pressure of 32 mm Hg, and mean pulmonary artery pressure of 40 mm Hg. Pulmonary capillary wedge pressure was 9 mm Hg, right atrial pressure was 12 mm Hg, and cardiac output was 3.43 L/min, corresponding to a cardiac index of 1.84 L/min/m². Pulmonary vascular resistance was 8 Wood units (Table 1). The acute vasoreactivity test was negative.

A comprehensive diagnostic evaluation was performed to exclude alternative causes of pulmonary hypertension. Ventilation–perfusion scintigraphy indicated a low probability of pulmonary embolism, and no significant parenchymal lung disease was identified. Thoracic computed tomography demonstrated cardiomegaly and bilateral pleural effusions (Figure 2). Autoimmune testing, including antinuclear antibody (ANA), perinuclear antineutrophil cytoplasmic antibody (pANCA), cytoplasmic antineutrophil cytoplasmic antibody (cANCA), rheumatoid factor, antichromatin antibodies, SCL-70, RNP antibodies, Smith antibodies, SS-A, SS-B, and DNA antibodies, was negative. The NT-proBNP concentration was 940 pg/mL (reference range, 0–125 pg/mL), and the 6-minute walk distance was 290 m.

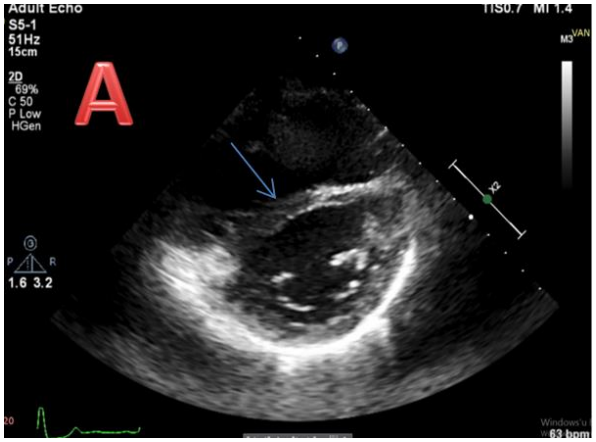
The clinical, echocardiographic, and hemodynamic findings were consistent with precapillary group 1 PAH. Given the absence of another identifiable cause, dasatinib-associated PAH was considered the most likely diagnosis.

Dasatinib was immediately discontinued after the diagnosis, and treatment with nilotinib was initiated as an alternative TKI. Nilotinib was maintained during follow-up without the development of further pulmonary complications. Prednisolone was administered for approximately 4 months because of the pleural effusion. PAH-targeted therapy was initiated with bosentan at 62.5 mg twice daily, followed by an increase to 125 mg twice daily.

At the 3-month assessment, the patient continued to experience significant dyspnea and fatigue. Her functional status corresponded to NYHA class II–III. Although the 6-minute walk distance had increased to 330 m and NT-proBNP had decreased to 540 pg/mL, systolic pulmonary artery pressure remained approximately 60 mm Hg on transthoracic echocardiography. Because she continued to meet an intermediate-risk profile despite bosentan therapy, riociguat was added at 1 mg 3 times daily and subsequently titrated according to clinical response and tolerability.

After 3 months of combined bosentan and riociguat treatment, a clear clinical improvement was observed. Dyspnea and fatigue decreased, and her functional status improved to NYHA class I–II. Her 6-minute walk distance increased to 410 m, while NT-proBNP decreased to 205 pg/mL (reference range, 0–125 pg/mL). Transthoracic echocardiography showed a reduction in systolic pulmonary artery pressure to 48 mm Hg. As the patient had transitioned to the low-risk category, the same treatment regimen was continued.

One year after initiation of combination therapy, repeat right heart catheterization was performed. The measurements demonstrated a pulmonary artery systolic pressure of 42 mm Hg, pulmonary artery diastolic pressure of 19 mm Hg, mean pulmonary artery pressure of 25 mm Hg, pulmonary capillary wedge pressure of 8 mm Hg, right atrial pressure of 8 mm Hg, and cardiac output of 4.8 L/min. Pulmonary vascular resistance remained elevated at 4 Wood units (Table 2). Although there had been substantial clinical and hemodynamic improvement, pulmonary hypertension persisted. Because the patient remained in the low-risk category, the existing treatment was continued.



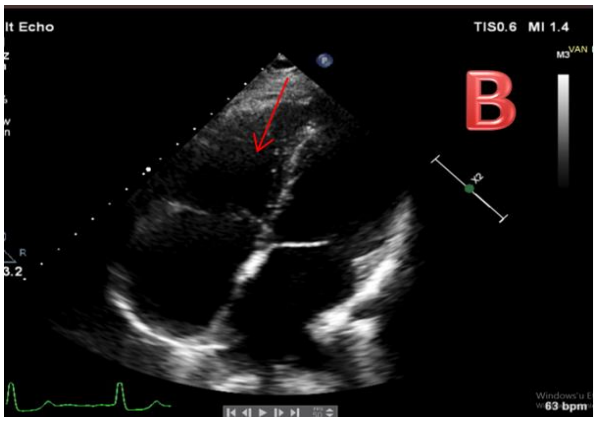


Figure 1. Transthoracic echocardiography of the patient showed a D-shaped configuration of the interventricular septum (blue arrow, panel A) and enlarged right heart dimensions (red arrow, panel B).

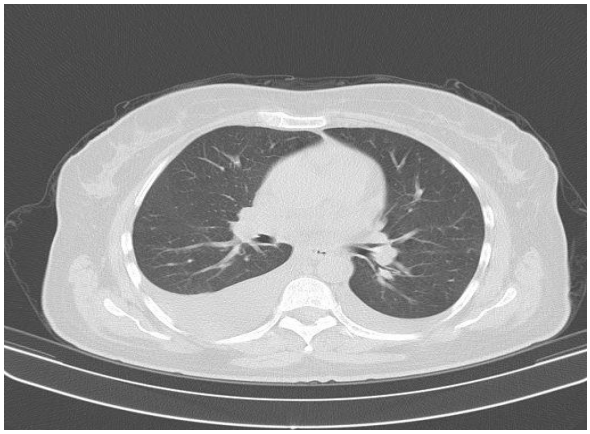


Figure 2. Thoracic computed tomography showed bilateral pleural effusion.

Table 1: Right heart catheterization measurments of the patient show high risk criteria

sPAP (mmHg)	60
dPAP (mmHg)	32
mPAP (mmHg)	40
PCWP (mmHg)	9
RA pressure (mmHg)	12
Cardiac Output (CO) (L/min)	3,43
Cardiac Index (L/min/m^2)	1,84
Pulmonary Vascular Resistance(PVR) (Woods Unit)	8

Table 2: One year after combination therapy right heart catheterization measurments showed irreversibility

sPAP (mmHg)	42
dPAP (mmHg)	19
mPAP (mmHg)	25
PCWP (mmHg)	8
RA pressure (mmHg)	8
Cardiac Output (CO) (L/min)	4,8
Cardiac Index (L/min/m^2)	1,84
Pulmonary Vascular Resistance(PVR) (Woods Unit)	4

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Discussion and Conclusions

The widespread use of BCR-ABL TKIs has transformed CML from a previously fatal hematological malignancy into a disease that can be effectively controlled over the long term. Dasatinib is a potent second-generation TKI that has demonstrated efficacy in the treatment of CML.[4,5] Nonetheless, prolonged exposure may be associated with clinically relevant adverse effects, making recognition and monitoring of treatment-related complications particularly important.

Among the BCR-ABL TKIs, dasatinib has been particularly associated with pulmonary toxicity. Pleural effusion is the most frequently recognized pulmonary complication, with reported rates ranging from approximately 15% to 35%.[6,7] Other pulmonary adverse events, including interstitial pneumonitis and PAH, have also been described. In contrast to pleural effusion, dasatinib-associated PAH is uncommon but may have substantial clinical consequences. The first reported case was published in 2009,1 and subsequent observational data have provided further evidence supporting the association.

In one French cohort, dasatinib-induced PAH was reported in 13 of 2900 symptomatic patients, corresponding to an estimated incidence of 0.45%.[8] Our patient developed both bilateral pleural effusion and pulmonary hypertension after 5 years of dasatinib exposure. The pleural effusion subsequently resolved following corticosteroid treatment.

The biological mechanisms responsible for dasatinib-associated PAH have not been fully elucidated. Inhibition of Src-family kinases has been proposed as one possible mechanism contributing to pulmonary vascular remodeling and dysfunction. Importantly, discontinuation of dasatinib does not invariably result in complete resolution of PAH. Although many patients experience substantial clinical and biochemical improvement after withdrawal of the drug, a subset may continue to demonstrate pulmonary vascular disease and require PAH-specific treatment.

Long-term follow-up data support the possibility of persistent disease. In a French pulmonary hypertension registry, approximately 37% of patients continued to have PAH despite discontinuation of dasatinib after a median follow-up of 24 months.[9] This observation emphasizes the importance of continued clinical and hemodynamic surveillance even when symptoms improve following withdrawal of the offending agent.

In our patient, bosentan was initiated after dasatinib discontinuation. The drug was selected as the initial PAH-targeted therapy, with the dose subsequently increased to 125 mg twice daily. After 3 months, however, the patient remained symptomatic and continued to have an intermediate-risk profile. Riociguat was therefore added to the treatment regimen.

Although phosphodiesterase-5 inhibitors, particularly sildenafil, have more frequently been described as additional therapy in patients with dasatinib-associated PAH[10], riociguat was selected in this case because persistent group 1 PAH was suspected despite initial treatment. The ability to titrate riociguat according to treatment tolerance and clinical response was considered an additional advantage. The treatment strategy also took into account the patient's ongoing hematological therapy and the possibility of drug-drug interactions.

Bosentan was chosen as the initial endothelin receptor antagonist based on treatment availability and institutional experience, as well as the possibility of subsequent dose escalation. Potential interactions with nilotinib were recognized, and the patient was monitored closely throughout follow-up.

The addition of riociguat was followed by a marked improvement in symptoms, functional capacity, exercise tolerance, and biomarkers. The patient’s risk profile consequently shifted from intermediate to low. Nevertheless, repeat right heart catheterization after 1 year demonstrated that pulmonary hypertension had not completely resolved. Although mean pulmonary artery pressure and pulmonary vascular resistance had substantially decreased compared with baseline, PVR remained elevated at 4 Wood units.

This case therefore illustrates an important distinction between clinical recovery and complete resolution of pulmonary vascular disease. The patient’s symptoms improved considerably with withdrawal of dasatinib and subsequent combination PAH therapy, but invasive

hemodynamic assessment demonstrated persistent abnormalities. She has remained clinically stable in the low-risk category for approximately 18 months while receiving combined bosentan and riociguat therapy.

In conclusion, dasatinib-associated PAH may persist even after discontinuation of the causative drug and apparent clinical improvement. Early recognition of pulmonary hypertension, prompt withdrawal of dasatinib, and individualized PAH-targeted therapy are important components of management. In selected patients who do not respond adequately to initial treatment, the addition of riociguat to bosentan may provide further clinical and hemodynamic benefit. Clinicians should maintain a high degree of clinical suspicion for PAH in patients receiving dasatinib who develop unexplained dyspnea, peripheral edema, or pleural effusion.

Declarations:

Ethical Approval

Ethical approval was not required for conducting this research.

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Conflict of Interest

The authors report no conflict of interest.

Acknowledgments

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