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CASE REPORT
Other

Dasatinib-induced pulmonary arterial hypertension complicated with scleroderma: a case report

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Background Although the BCR-ABL tyrosine kinase inhibitor dasatinib is a potent treatment for chronic myeloid leukaemia, it is associated with the risk of dasatinib-induced pulmonary arterial hypertension (DASA-PAH), for which predisposing factors have yet to be elucidated. However, animal studies have shown that dasatinib exacerbates pulmonary hypertension (PH) in rodent models of PH but not in controls, providing support for a two-hit theory of DASA-PAH pathophysiology.

Case summary A 63-year-old man with worsening dyspnoea was diagnosed with severe DASA-PAH and concomitant scleroderma. He was successfully treated with discontinuation of dasatinib and administration of pulmonary vasodilators.

Discussion Our case suggests that scleroderma may be a predisposing factor for the development of DASA-PAH, providing new insight into its pathophysiology.

Keywords Case report • Dasatinib • BCR-ABL tyrosine kinase inhibitor • Pulmonary arterial hypertension • Scleroderma

Learning points

- Dasatinib-induced pulmonary arterial hypertension (DASA-PAH) is a rare complication of dasatinib administration with unclear predisposing factors. We report a case of severe DASA-PAH complicated with scleroderma that was successfully treated with dasatinib discontinuation and pulmonary vasodilators.
- Our case provides support for the two-hit hypothesis of DASA-PAH development and demonstrates how this condition can be treated.
- It is crucial to screen patients undergoing dasatinib treatment with regular echocardiographic surveillance for the early detection of DASA-PAH.

Introduction

The second generation BCR-ABL tyrosine kinase inhibitor (TKI) dasatinib is a potent treatment for chronic myeloid leukaemia (CML) and Philadelphia chromosome-positive acute lymphoid leukaemia.[1] However, growing evidence suggests that dasatinib can cause drug-induced pulmonary arterial hypertension (PAH), with more than 100 cases of dasatinib-induced PAH (DASA-PAH) having been reported.

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Despite this, the predisposing factors for DASA-PAH remain indeterminate.[2] Herein, we present a case of severe PAH with concomitant scleroderma that developed during dasatinib treatment. The patient was successfully managed with dasatinib withdrawal and upfront triple pulmonary vasodilator combination therapy, providing novel support for a two-hit hypothesis of DASA-PAH development.

Timeline

8 years prior to presentation	Chronic myeloid leukaemia diagnosed at clinic. Imatinib (400 mg o.d.) initiated.
5 years prior to presentation	Imatinib withdrawn due to facial oedema and massive pleural effusion. Dasatinib (100 mg o.d.) initiated.
Initial presentation	Patient presented with a 2-year history of dyspnoea that had worsened in the previous 6 months. Pulmonary hypertension diagnosed at clinic based on electrocardiography, transthoracic echocardiography, and contrast-enhanced chest computed tomography.
Day 2	Pulmonary arterial hypertension (PAH) diagnosed on admission based on scintigraphy and right heart catheterization (RHC). Dasatinib withdrawn. Tadarafil (40 mg o.d.), macitentan (10 mg o.d.), and selexipag (1.2 mg b.i.d.) initiated.
1 month	Prompt improvement in PAH.
4 months	Imatinib (300 mg o.d.) initiated.
Follow-up (1 year)	No PAH as indicated by RHC. Selexipag withdrawn.

Case presentation

A 63-year-old man presented to our department with exertional dyspnoea. He had a 2-year history of dyspnoea that had worsened over the previous 6 months. He had also been diagnosed with CML at the age of 55, for which a first-generation TKI, imatinib (400 mg daily), was prescribed as his first-line therapy. However, since this caused facial oedema and massive pleural effusion, a second-generation TKI, dasatinib (100 mg daily), was chosen as his second-line therapy 5 years before presentation. Concomitant pleural effusion and anaemia was thought to have caused the dyspnoea 2 years prior to presentation; subsequently, an additional dose of diuretics and a reduced dose of dasatinib (50 mg daily) resulted in a transient improvement of dyspnoea following a decrease in the amount of pleural effusion and a slight increase in haemoglobin without further evaluation.

Electrocardiography (*Figure 1*) and transthoracic echocardiography (TTE) (*Figure 2A*, *Table 2*) on admission indicated severe right ventricular pressure overload. Physical examination showed jugular vein dilatation. His lung sounds were normal, but cardiac auscultation revealed increased intensity of the P2 sound. The liver was slightly enlarged, but splenomegaly was unclear. Laboratory data showed markedly elevated brain natriuretic peptide (442 pg/mL; normal reference value, <18.4 pg/mL), and anti-nuclear and anti-centromere antibody positivity (1280X and 166X, respectively). Contrast-enhanced chest computed tomography showed no evidence of pulmonary embolism, and perfusion-ventilation scintigraphy showed no evidence of segmental mismatch. Neither abdominal ultrasonography nor upper endoscopy showed clear evidence of portal hypertension. Right heart catheterization (RHC) confirmed markedly increased mean pulmonary artery pressure (MPAP; 67 mmHg; normal reference value, ≤20 mmHg[3]) and pulmonary vascular resistance [PVR; 23.5 wood units (WU); normal reference value, ≤3 WU[3]] on room air (*Table 1*). Because the patient presented with Raynaud's phenomenon and nail fold bleeding, a skin biopsy was performed. Pathological findings included increased collagen fibres in subcutaneous adipose tissue and the dermis, increased mucin deposits between collagen fibres, and infiltration of inflammatory cells (mainly lymphocytes) around vessels, supporting a diagnosis of scleroderma. Neither DASA-PAH nor scleroderma-associated PAH (SSc-PAH) could be defined as the primary cause of PAH.

Based on these findings, we simultaneously discontinued dasatinib and started initial combination therapy with the pulmonary vasodilators, tadalafil (40 mg daily), macitentan (10 mg daily), and selexipag (1.2 mg twice daily). RHC 1 month later showed improvement of the patient's MPAP and PVR to 35 mmHg and 5.7 WU, respectively (*Table 1*), with his 6-min walk distance also improving from 20 m to 490 m. RHC at 3 months demonstrated further improvement of MPAP and PVR to 33 mmHg and 3.9 WU, respectively. Serial TTEs performed at 1 and 3 months also revealed improved right ventricular pressure overload (*Figure 2B* and *C*, *Table 2*). At 4 months, as the Philadelphia chromosome became detectable, TKI administration with imatinib (300 mg daily) was resumed at a lower dose than previously prescribed. At 1 year, MPAP and PVR improved to reasonable values of 18 mmHg and 1.3 WU, respectively. We then withdrew selexipag from the treatment regimen without any evidence of clinical worsening.

Discussion

BCR-ABL TKIs such as dasatinib are potent drugs that have transformed CML from a lethal to controllable disorder, though growing evidence suggests that dasatinib induces PAH. Although the prevalence of clinically significant DASA-PAH is speculated to be as low as 0.45–3%,[4–6] its occurrence requires dasatinib withdrawal, leading to an increased risk of CML recurrence as in our case. The current European Society of Cardiology guideline recommends TTE surveillance once every 3 months during dasatinib treatment.[3] We must therefore focus on early detection of PAH to avoid interruption of CML treatment.

Despite being a BCR-ABL TKI, dasatinib is also a potent inhibitor of Src kinases,[7] as Src kinase inhibition could be involved in DASA-PAH development.[5] However, Guignabert *et al.*[8] reported that dasatinib treatment induces pulmonary endothelial cell apoptosis in a dose-dependent manner and endothelial dysfunction via increased production of reactive oxygen species, which occur independently of Src kinases. These authors also demonstrated that dasatinib

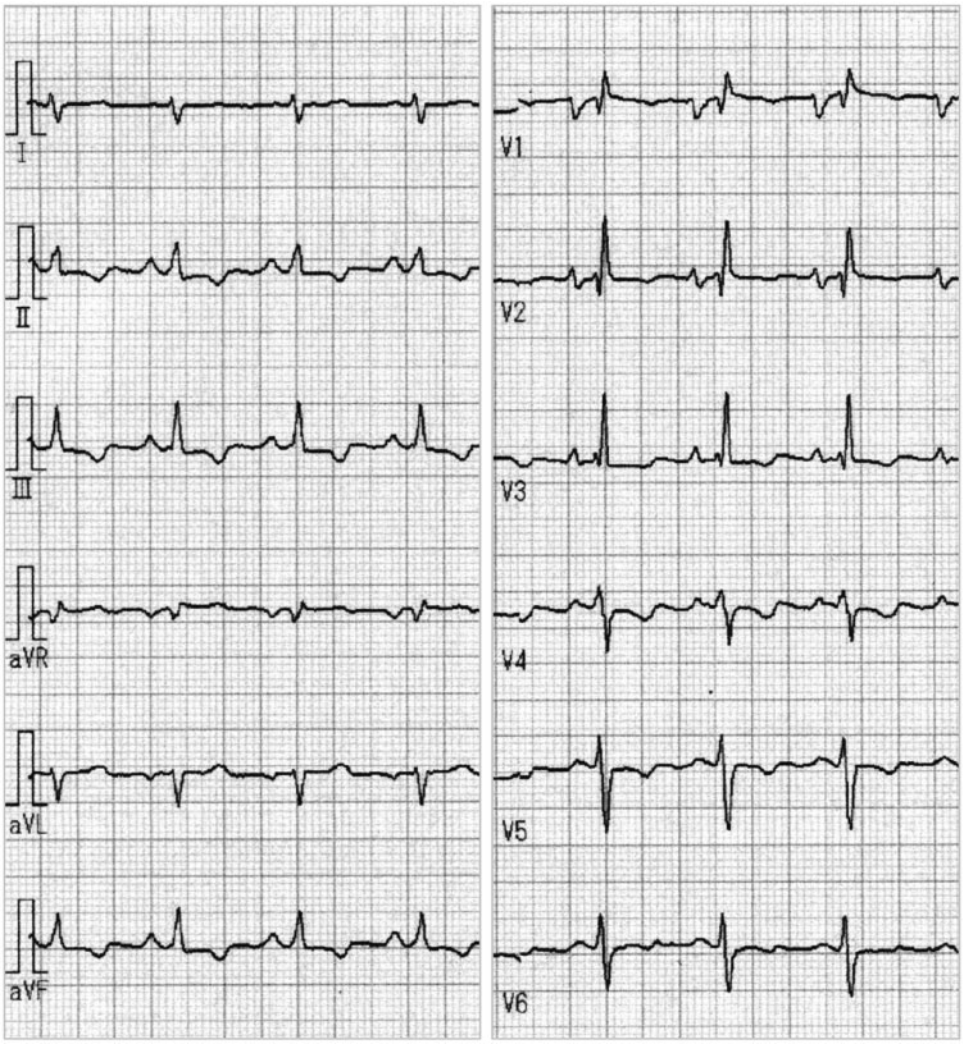

Figure 1 Electrocardiogram (ECG) findings at initial presentation. An electrocardiogram revealed an incomplete right bundle branch block; an R/S ratio >1 in lead V1; T wave inversion in leads II, III, aVF, and V1–V5; and an R wave in lead V1 + S wave in lead V5 amplitude sum >10.5 mm, indicating right ventricular hypertrophy.

exacerbates PAH only in a rodent model of PAH but not in control animals, supporting a two-hit theory of the pathophysiology of DASA-PAH. We have also identified human studies that appear to support this hypothesis. In a report of 41 patients with RHC-confirmed DASA-PAH, 94% showed improvement, but only 58% achieved complete resolution.[4] Moreover, among nine DASA-PAH patients reported in the French pulmonary hypertension registry, eight showed significant clinical, functional, and haemodynamic improvement following dasatinib withdrawal, despite only three receiving pulmonary vasodilators. However, none returned to normal haemodynamic status.[5] Taken together, these data indicate the existence of underlying predisposing factors for DASA-PAH other than dasatinib drug toxicity, supporting the two-hit theory.

These predisposing factors, however, remain unidentified, though PAH is known to be an independent risk factor for mortality in patients with scleroderma.[9] Despite early diagnosis and treatment using pulmonary vasodilators, the therapeutic effects of these drugs and survival rates in patients with SSc-PAH are worse than in those with idiopathic PAH.[10] Indeed, among the REVEAL Registry cohort, 3-year survival rates were worse in newly diagnosed SSc-PAH patients than in those with other connective tissue diseases (51.2% vs. 76.4%), even though approximately one-third of patients in both groups were on multiple pulmonary vasodilators.[11] Furthermore, a prospective cohort study of 794 scleroderma patients reported worse 2-year survival rates in patients with MPAP >45 mmHg than in those with MPAP <32 mmHg (39% vs. 78%).[12] In our patient, whose initial MPAP was 67 mmHg, clinical symptoms and haemodynamic status promptly improved following cessation of dasatinib and the initiation of triple pulmonary vasodilator combination therapy. This indicates that the patient's PAH was unlikely to be secondary to his scleroderma, but rather that his scleroderma might have predisposed him to developing DASA-PAH.

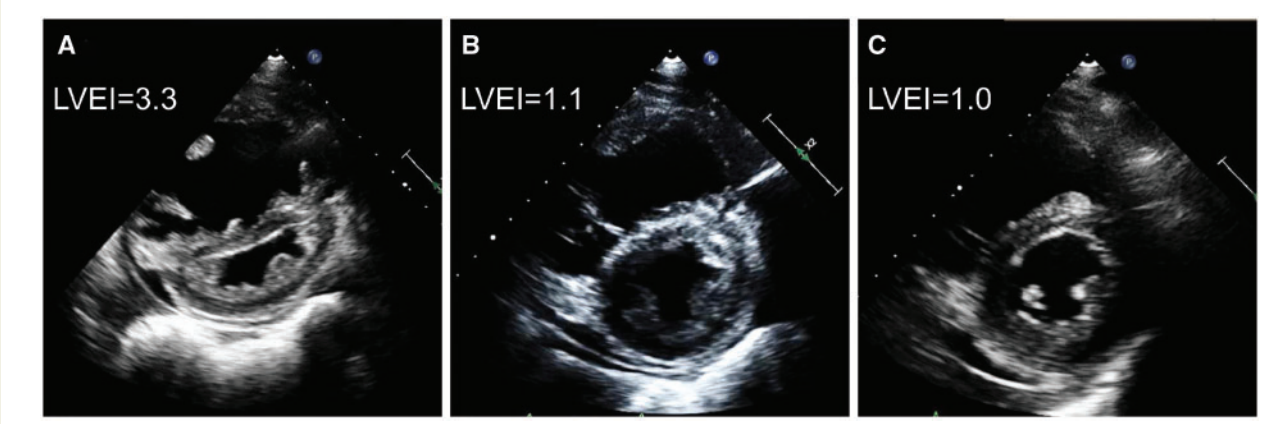

Figure 2 Transthoracic echocardiography. The parasternal short-axis view is shown at (*A*) initial presentation, (*B*) 1 month after dasatinib withdrawal, and (*C*) 3 months after dasatinib withdrawal. LVEI, left ventricle eccentricity index.

Table 1 Haemodynamic findings

	Initial		1 month	3 month		12 month	
	Room air	Oxygen	Room air	Room air	Oxygen	Room air	Oxygen
SPAP/DPAP (mmHg)	94/49	83/42	57/25	50/22	41/17	26/12	24/9
MPAP (mmHg)	67	58	35	33	27	18	16
PAWP (mmHg)	14	16	7	11	12	9	7
SAP/DAP (mmHg)	127/95	117/93	103/72	96/59	105/61	129/78	127/72
MRAP (mmHg)	15	16	4	8	5	4	3
PVR (WU)	23.5	17.8	5.73	3.94	2.53	1.33	1.26
CO (L/min)	2.25	2.36	4.88	5.59	5.92	6.77	7.12
CI (L/min/m^2)	1.35	1.41	2.92	3.34	3.54	3.96	4.17
SaO_2 (%)	93.2	97.8	90.0	93.1	98.4	93.7	99.2
SvO_2 (%)	45.5	53.6	68.5	70.5	77.5	70.8	78.8

CO, cardiac output; CI, cardiac index; DAP diastolic blood pressure; DPAP, diastolic pulmonary artery pressure; MPAP, mean pulmonary artery pressure; MRAP, mean right atrium pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; SaO_2, arterial oxygen saturation; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; SvO_2, mixed venous oxygen saturation; WU, wood units.

Table 2 Echocardiographic measurements

	Initial	1 month	3 month
RVSP (mmHg)	86	55	28
RV fractional area change (%)	14.8	27.6	34.0
LV eccentricity index	3.3	1.1	1.0
S' wave of tricuspid annulus (cm/s)	7.3	13.8	15.0
TAPSE (cm)	1.3	2.3	2.5

LV, left ventricle; RV, right ventricle; RVSP, right ventricular systolic pressure; S' wave, systolic wave; TAPSE, tricuspid annular plane systolic exertion.

Regarding management, a treatment strategy for DASA-PAH has not been determined, with dasatinib discontinuation only reversing pulmonary arterial pressure and PVR in some reports.[13] Recently, Weatherald *et al.*[2] reported long-term outcomes in 21 patients treated for DASA-PAH. Dasatinib was discontinued in all patients and pulmonary vasodilators were prescribed in 11; those treated with pulmonary vasodilators had worse baseline haemodynamics but could reach long-term haemodynamic outcomes similar to those in patients not treated with pulmonary vasodilators, though PAH persisted in 37% at the last follow-up (median 24 months). The authors proposed a similar treatment algorithm to ours; that is, to treat patients presenting with more severe symptoms [e.g. New York Heart Association (NYHA) functional class (FC) III or IV] and those with severe haemodynamic compromise [e.g. cardiac index (CI) <3 L/min/m^2] with pulmonary vasodilators, and to consider de-escalation of pulmonary vasodilators if normal haemodynamics persists at 1 year. In our case, the patient's initial presentation was severe (i.e. NYHA FC IV and CI 1.35 L/min/m^2); therefore,

his treatment with multiple pulmonary vasodilators was justified and eventually shown to be successful.

In conclusion, we experienced a case of DASA-PAH complicated with scleroderma that provides novel support for the two-hit hypothesis of DASA-PAH pathophysiology. However, further research is necessary to identify its predisposing factors and facilitate its early detection.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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