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CASE REPORT
Heart failure

Comprehensive treatment strategy in a patient with systemic lupus erythematosus-related pulmonary artery hypertension: a case report

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Background Although the prognosis in systemic lupus erythematosus (SLE) has dramatically improved, pulmonary artery hypertension (PAH) is one of the life-threatening comorbidities associated with SLE. The management of the comorbidity is occasionally challenging due to the lack of consensus regarding treatment options including immunosuppressive agents, selective pulmonary vasodilators, and cardiac rehabilitation.

Case summary A 28-year-old female who terminated prednisolone after remission of SLE by her own discretion 3 years ago developed dyspnoea on effort. Transthoracic echocardiography showed dilatation of the right atrium (RA) and ventricle (RV), as well as the RV dysfunction. The findings of right heart catheterization and pulmonary perfusion scintigraphy confirmed PAH associated with connective tissue disease. According to the SLE Disease Activity Index (SLEDAI) and the REVEAL Registry Risk Score, she was at high risk of PAH despite mild SLE activity. Upfront combination therapy including macitentan and tadalafil for PAH and steroid semi-pulse and cyclophosphamide pulse therapy for SLE alongside supervised cardiac rehabilitation were initiated simultaneously. The RA and RV sizes were normalized after the aforementioned therapy. The RV–pulmonary artery (PA) coupling improved from 0.15 to 0.77 mm/mmHg, and the mean PA pressure decreased from 55 to 29 mmHg.

Discussion The case presentation highlighted the potential benefits of comprehensive treatment strategy including immunosuppressive treatment, upfront combination therapy, and supervised exercise training. Notably, the initiation of cardiac rehabilitation at the early phase did not exacerbate her condition and might have contributed to remission of symptoms and improvement in exercise tolerance. This multidisciplinary approach achieved long-term good quality of life.

Keywords Cardiac rehabilitation • Case report • Pulmonary artery hypertension • Systemic lupus erythematosus • Upfront combination therapy

ESC curriculum 9.6 Pulmonary hypertension • 6.7 Right heart dysfunction

Learning points

- Comprehensive treatment strategy including immunosuppressive treatment and upfront combination therapy can improve haemodynamic status in a patient with systemic lupus erythematosus-related pulmonary artery hypertension at high risk.
- Supervised cardiac rehabilitation during the early phase might be safe and contribute to remission of symptoms and improvement in exercise tolerance.

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Introduction

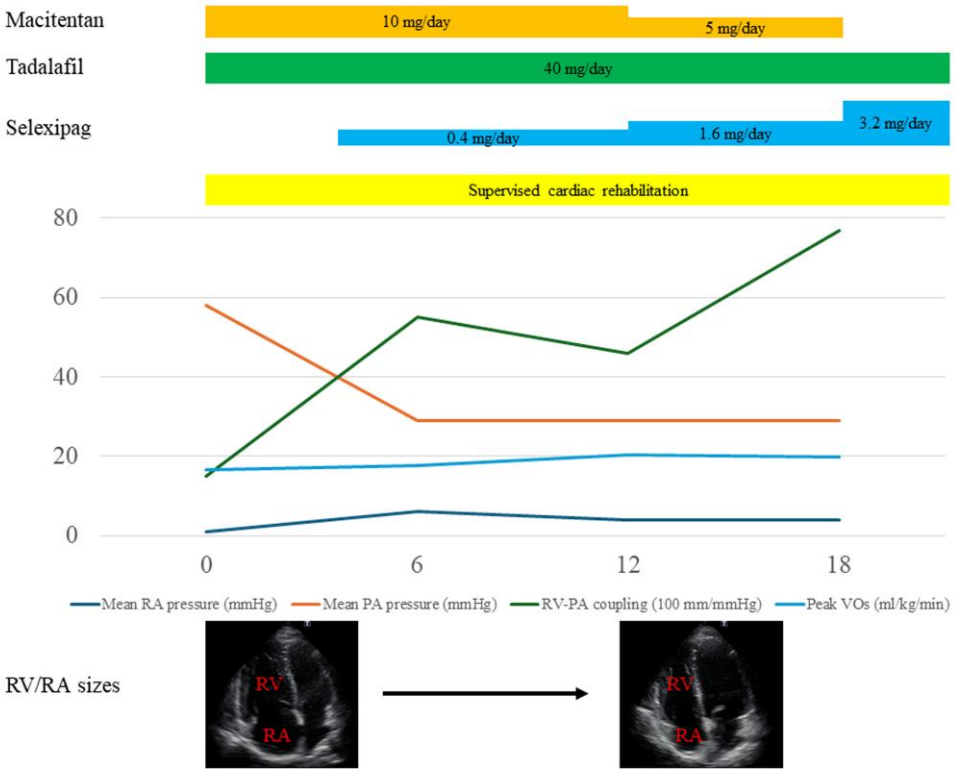
Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disorder characterized by multi-organ damage and systemic inflammatory lesions due to the tissue deposition of immune complexes.[1] The prognosis in SLE has dramatically improved and the five-year survival exceeded 90% since 1980,[2] probably owing to earlier diagnosis, treatment, and the evolution of medical therapy. However, SLE can indicate various clinical courses based on comorbidities. Pulmonary artery hypertension (PAH) is one of the life-threatening comorbidities associated with SLE. The management of such comorbidity is occasionally challenging due to the lack of consensus regarding treatment options including immunosuppressive agents, selective pulmonary vasodilators, or a combination of them. Optimal medical therapy has not been determined yet.[3] Furthermore, in some selected cases medication alone cannot achieve reversal of right ventricular (RV) dysfunction and normalization of the pulmonary vascular resistance (PVR). Non-pharmacological treatment such as cardiac rehabilitation may be a potential treatment option.[4]

In this report, we present an SLE-related PAH female patient with severe right ventricular dysfunction who walked level ground with dyspnoea. Through a multidisciplinary approach involving immunosuppressive therapy, selective pulmonary vasodilators, and cardiac rehabilitation, there was a significant reduction in the mean pulmonary artery (PA) pressure and normalization of the RV function. Remarkably, the patient's condition improved to the extent that she was able to engage in sports activities such as playing tennis.

Summary figure

Case presentation

A 28-year-old female was diagnosed with SLE 13 years ago and had been in remission with prednisolone, which was terminated by her own discretion 3 years ago. She was referred to our hospital because of dyspnoea on effort equivalent to New York Heart Association (NYHA) functional class III. An increased PA component of the second heart sound and the fourth heart sound was heard on auscultation. Her respiratory rate was 20 breaths per minute, and the oxygen saturation was 96% at rest. Her chest X-ray indicated an enlarged left PA and a protrusion of the right atrium (RA) (*Figure 1*). Blood examination showed mildly elevated transaminases, elevated BNP (450.8 pg/mL; the normal reference value: ≤18.4 pg/mL), and decreased serum complement titre (5 U/mL; the normal reference values: 30–45 U/mL). The anticardiolipin antibody value was 6.4 U/mL (the normal reference value: ≤12.3 U/mL), indicating a negative result. An electrocardiogram demonstrated sinus rhythm with a heart rate of 75 beats per minute. The overloads of the RA and RV were observed (*Figure 2*). Transthoracic echocardiography showed the dilated right atrium and ventricle, with an estimated systolic PA pressure (sPAP) of 118 mmHg (*Figure 3*). Severity of the tricuspid regurgitation was moderate (see Supplementary material online, *Video S1*). Tricuspid annular plane systolic excursion was 18 mm and RV–PA coupling was 0.15 mm/mmHg, suggesting RV dysfunction. She was hospitalized for an investigation of the cause of dyspnoea and its treatment. Right heart catheterization revealed a mean PA pressure of 55 mmHg, mean pulmonary capillary wedge pressure (PCWP) of 10 mmHg, PVR of 9.0 Wood units, and cardiac index of 1.4 L/min/m^2. Contrast-enhanced computed tomography demonstrated no evidence of pulmonary embolism during the acute phase (see Supplementary material online, *Figure S1*). Pulmonary perfusion scintigraphy showed



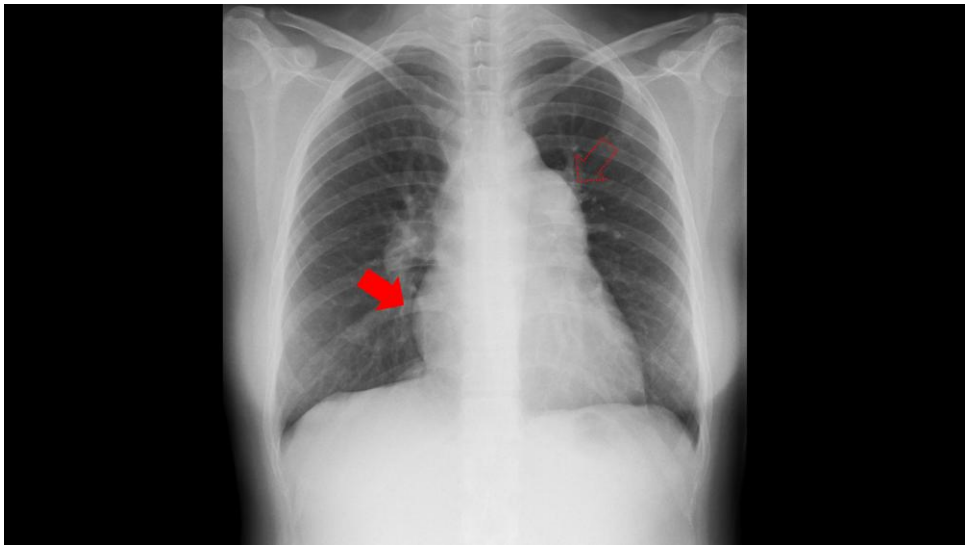


Figure 1 An initial chest X-ray. A chest X-ray indicated an enlarged left pulmonary artery (dotted arrow) and a protrusion of the right atrium (solid arrow), suggesting pulmonary hypertension.

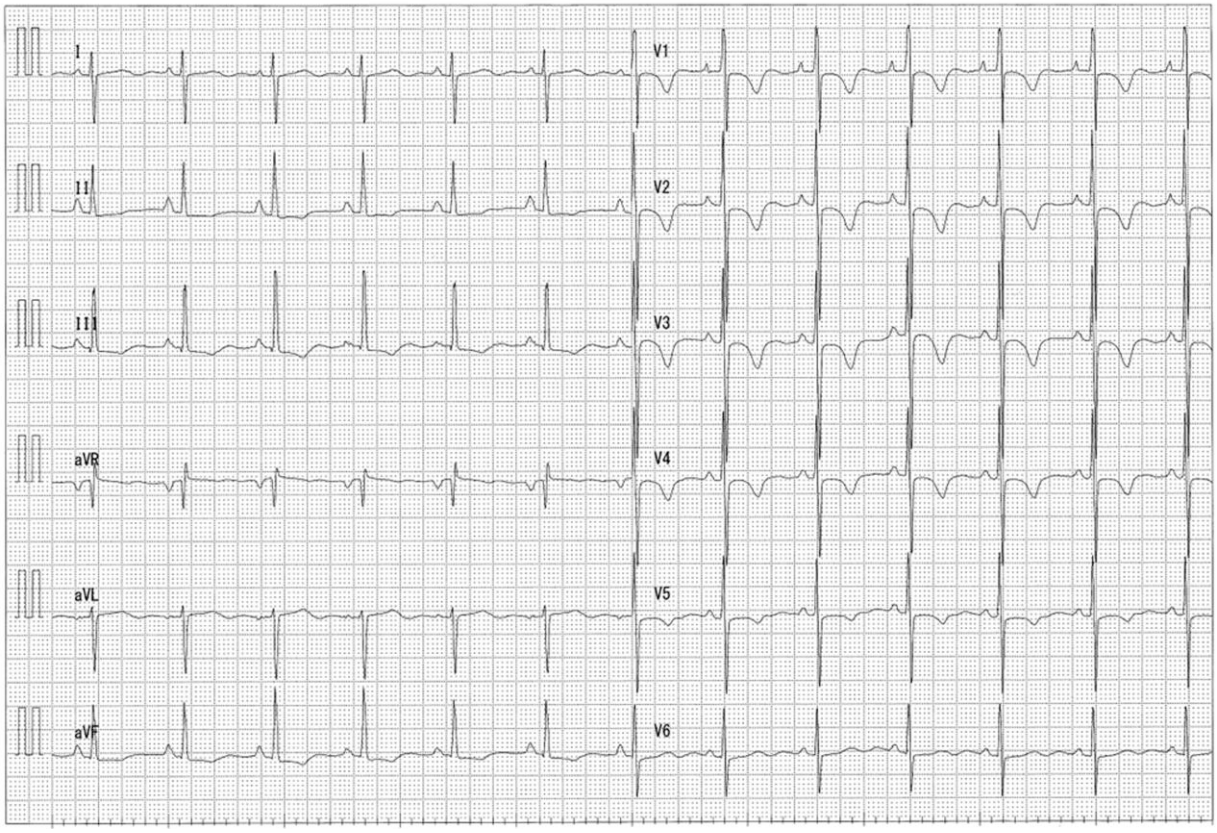


Figure 2 An initial electrocardiogram. An electrocardiogram demonstrated sinus rhythm with a heart rate of 75 beats per minute. Right atrial and ventricular load was noted.

no significant reduction in blood flow (see Supplementary material online, *Figure S2*). The patient was diagnosed as PAH associated with connective tissue disease.

The SLE Disease Activity Index (SLEDAI) was 2, while the REVEAL Registry Risk Score was 9 points and TAPSE/sPAP was 0.15 mm/mmHg; namely, the patient was at high risk of PAH despite mild SLE activity. It was unlikely that immunosuppressive therapy alone could provide a sufficient decrease of PA pressure. Therefore, multidisciplinary treatment for SLE and PAH was initiated. Pulmonary artery hypertension was treated with upfront combination therapy including macitentan and tadalafil. Steroid semi-pulse and cyclophosphamide pulse therapy were administered for SLE, followed by oral prednisolone and hydroxychloroquine. Given the negative result of anticardiolipin antibody, anticoagulation was not administrated. Simultaneously, supervised cardiac rehabilitation was also initiated. One week after such treatment, the 6 min walk test improved from 248 m at baseline to 400 m. Right heart catheterization 3 months later showed significant improvement with a mean PA pressure of 29 mmHg. NYHA functional class was I, REVEAL Registry Risk Score was 5 points, and TAPSE/sPAP improved to 0.55 mm/mmHg. Further, transthoracic echocardiography showed normalization of RA and RV sizes, (*Figure 4*) leading to the disappearance of tricuspid regurgitation (see Supplementary material online, *Video S2*). Summary of PAH-related parameters before and after the treatment is shown in *Table 1*. RV function and exercise tolerance have improved

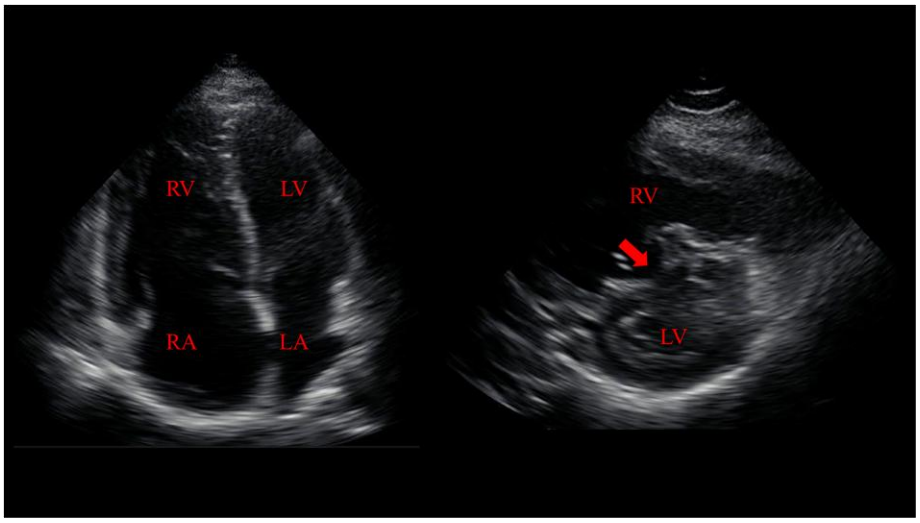


Figure 3 The RV overload prior to medical treatment. The findings on the echocardiogram were recorded during the diastolic phase. The apical four-chamber view revealed significant dilation of the RA and RV (left panel). Compression of the interventricular septum (solid arrow) was noted due to the RV overload (right panel). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

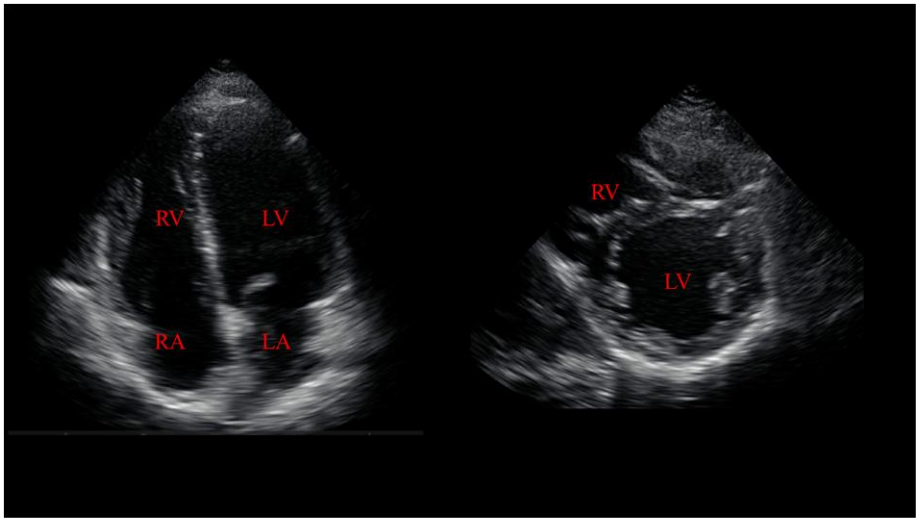


Figure 4 Reverse remodelling of the RV. The echocardiogram at one year after comprehensive treatment demonstrated that reverse remodelling of the RV and RA. Compression of the interventricular septum disappeared. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Table 1 **Pulmonary perfusion scintigraphy demonstrated no significant reduction in blood flow**

	Before treatment	1 month later	3 months later	10 months later	12 months later	18 months later
Macitentan	0	10 mg once a day	10 mg once a day	10 mg once a day	5 mg once a day	0
Tadalafil	0	20 mg twice a day	20 mg twice a day	20 mg twice a day	20 mg twice a day	20 mg twice a day
Selexipag	0		0.2 mg twice a day	0.8 mg twice a day	0.8 mg twice a day	1.6 mg twice a day
Mean RA pressure (mmHg) (NRV: 1–5 mmHg)	1		6		4	
Systolic PA pressure (mmHg) (NRV: 15–30 mmHg)	100		45		44	
Diastolic PA pressure (mmHg) (NRV: 4–12)	38		21		17	
Mean PA pressure (mmHg) (NRV: <25 mmHg)	55		29		29	
Mean PCWP (mmHg) (NRV: <15 mmHg)	10		18		19	
PVR (dyn/s/cm^5) (NRV: <180 dyn/s/cm^5)	717		178		134	
PVR (Wood unit) (NRV: <2 Wood units)	9.0		2.2		1.7	
CI (L/min/m^2) (NRV: >2.5 L/min/m^2)	3.00		3.01		3.79	
LVEF (%) (NRV: ≥50%)	63		63	61	64	65
E wave (cm/s)	36		63	80	89	80
A wave (cm/s)	48		36	37	31	28
E/A (NRV: 0.8–1.5)	0.76		1.77	2.15	2.86	2.86
Deceleration time (ms) (NRV: 150–240 ms)	377		259	163	175	169
Fractional area change (%) (NRV: <35%)	19		39	44	45	40
Tissue Doppler imaging (s′) (cm/s) (NRV: 5.6–10.8 cm/s)	9.2		12.5	11.6	11.5	11.0
TAPSE (mm) (NRV: ≥17 mm)	18		21	22	20	19
Estimated SPAP (mmHg) (NRV: 15–30 mmHg)	117		38.4	30.3	43.6	24.6
RV–PA coupling (mm/mmHg) (NRV: >0.55 mm/mmHg)	0.15		0.55	0.73	0.46	0.77

Continued

Table 1 *Continued*

	Before treatment	1 month later	3 months later	10 months later	12 months later	18 months later
Serum creatinine (mg/dL) (NRV: 0.50–0.90 mg/dL)	0.60	0.74	0.58	0.59	0.50	0.60
eGFR (mL/min/1.73m^2) (NRV: ≥60 mL/min/1.73 m^2)	96.3	76.6	100.0	97.1	116.4	94.5
Total bilirubin (mg/dL) (NRV: 0.3–1.0 mg/dL)	1.1	0.6	0.4	0.6	0.3	0.4
AST (IU/L) (NRV: 13–30 IU/L)	35	29	17	18	17	20
ALT (IU/L) (NRV: 7–23 IU/L)	39	53	21	14	17	13
γGTP (IU/L) (NRV: 9–32 IU/L)	22	31	26	15	16	16
Alkaline phosphatase (IU/L) (NRV: 38–113 IU/L)	71	35	45	42	33	36
VO_2 at AT (mL/kg/min)		12.1	11.1	13.8		10.9
Peak VO_2 (mL/kg/min)		16.6	17.6	20.3		19.7
Exercise tolerance (METs)		4.7	5.0	5.8		5.6

AT, anaerobic threshold; CI, cardiac index; METs, metabolic equivalents; NRV, normal reference value; PA; pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; RV; right ventricle; VO_2, oxygen consumption.

10 months after the upfront combination therapy. Because of hope for pregnancy, she requested discontinuation of macitentan. Gradual reduction of the agent with up-titration of selexipag did not increase both mean PA and RA pressure, while a temporal reduction in TAPSE/sPAP without exacerbation of dyspnoea was observed. Peak maximal oxygen consumption (VO_2) improved from 16.6 to 19.7 mL/kg/min. The PVR decreased from 9.0 to 1.7 Wood units; however, the mean PA pressure remained at 29 mmHg even after the normalization of PVR. The mean PCWP increased from 10 to 19 mmHg at 12 months. The E/A ratio and deceleration time at 3 and 12 months were 1.77 and 259 ms, and 2.86 and 175 ms, respectively, suggesting that she could be in the process of developing left ventricular diastolic dysfunction. Another possibility is that the reduction in PVR might increase preload, leading to a rise in PCWP. She had no signs of left-sided heart failure.

Discussion

In this case report, a combination of immunosuppressive agents and pulmonary vasodilators improved the symptoms and echocardiographic findings in a female patient with SLE-related PAH at a high risk of mortality. Further, supervised cardiac rehabilitation ameliorated her exercise tolerance. Notably, she did not undergo any exacerbations during switching from a prescription of macitentan to selexipag, or exercise training.

Although previous randomized controlled trials demonstrated that a supervised exercise training regimen improved exercise capacity and quality of life in PAH patients,[5,6] there is still a concern that exercise training could increase wall shear stress on the pulmonary vessels, evoke pulmonary vascular remodelling, and worsen the disease, especially in patients with severe PAH. Therefore, rehabilitation should be introduced to stable patients with pulmonary vasodilators.[7]

Although the patient was expected to have a worse prognosis based on the REVEAL Registry Risk Score, her clinical course has been favourable. This case offers important lessons for cardiologists treating PAH patients with poor exercise tolerance. First, a combination therapy of immunosuppressive agents and pulmonary vasodilators did not yield any complications. While the current guideline recommends the same treatment algorithm for patients with connective tissue disease-related PAH as for those with idiopathic pulmonary arterial hypertension,[8] it remains unclear whether the immunosuppressive agents and pulmonary vasodilators should be prescribed simultaneously. The patient underwent a rapid decrease in mean PA pressure and PVR, alongside an improvement in RV function, all of which suggest potential benefits from the aforementioned comprehensive treatment strategy. Among these treatments, immunosuppressive therapy might prevent the exacerbation of SLE and avoid further progression of PAH, while pulmonary vasodilators would directly improve haemodynamics.

Second, supervised cardiac rehabilitation appeared to improve peak VO_2 without exacerbation of haemodynamic status after an initiation of pulmonary vasodilators. While the patient's peak VO_2 improved, VO_2 at anaerobic threshold (AT) did not. Considering the clinical course, the cardiac rehabilitation programme might contribute more significantly to muscle gain than to improvement in cardiopulmonary function. VO_2 at AT might be affected by pulmonary vasodilators because the value was highest when she was taking three types of agents. Currently, reimbursement for exercise training for patients with PAH is limited to only a few countries.[4] This may be attributed to the lack of a clearly defined optimal setting for rehabilitation.

Third, the up-titration of selexipag enabled the discontinuation of macitentan, which is contraindicated during pregnancy, for stable PAH patients who desired to conceive. However, considering the temporal exacerbation of the RV–PA coupling, cardiologists should carefully consider the timing of switching between these agents. She did not develop dyspnoea during the RV–PA coupling decreased, indicating that RV dysfunction can progress silently.

We should carefully monitor and treat the patient if she will become pregnant. Despite improvement in prognosis due to progress in medical treatment, maternal mortality remains high, ranging from 11 to 25%.[9] Pulmonary artery hypertension patients may worsen at any time during and after pregnancy. Further, pregnancy can exacerbate not only PAH, but also SLE. Active SLE increases the risk of adverse events, including lupus flares.[10] European Society of Cardiology/European Respiratory Society guidelines in 2022 propose alternatives such as adoption and surrogacy,[9] both of which are safe for PAH females. However, surrogacy is not permitted by the Japanese Government. Closed individual counselling and shared decision making are required.

In conclusion, the case presentation highlighted the potential benefits of comprehensive treatment strategy including immunosuppressive treatment, upfront combination therapy, and supervised exercise training, all of which contributed to haemodynamic stabilization, remission of symptoms, and improvement in exercise tolerance.

Lead author biography

Miku Yokoe is currently working as a resident at Seirei Mikatahara General Hospital in Shizuoka, Japan. She graduated from Showa University School of Medicine in 2024.

Supplementary material

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

Consent: The authors confirm that written consent for submission and publication of this case report, including the use of images and laboratory data, has been obtained from the patient in accordance with COPE guidelines.

Conflict of interest: None declared.

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Data availability

The authors confirm that the data supporting the findings of this case report are available within the article and its supplementary materials.

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