

CASE REPORT

ADVANCED

CLINICAL CASE

Interferon- β -Induced Pulmonary Arterial Hypertension



Approach to Diagnosis and Clinical Monitoring

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ABSTRACT

A 48-year-old woman who had been receiving long-term interferon- β for 8 years for multiple sclerosis developed drug-induced World Health Organization group I pulmonary arterial hypertension. Triple therapy for pulmonary arterial hypertension and suspension of interferon- β led to improvement from a high-risk to low-risk state and improvement in exercise hemodynamics, including vascular distensibility, and right ventricle-pulmonary artery coupling. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:1038-43) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Pulmonary arterial hypertension (PAH) is a rare disease, and drug-induced PAH constitutes nearly 10.5% of PAH cases (1). Since the first report of drug-induced PAH with anorexic agents in 1965, multiple putative PAH-inducing drugs have

been identified and classified into 3 categories: definite, likely, and possible. The 2 types of interferons (IFN- α and IFN- β) are classified into the “possible” category (2). Of the 2 IFNs, IFN- β (used for multiple sclerosis [MS]) has been less commonly reported to induce PAH; when it does, the disease course is less predictable (2). As in other forms of PAH, the prognosis is determined by the vasodilatory response of the pulmonary arterial (PA) circulation with exercise, adaptation of the right ventricle to the increased afterload, and right ventricular (RV) function (3,4). To quantify these aspects of pulmonary vascular and cardiopulmonary function, novel methods of pulmonary vascular distensibility and RV-PA coupling assessment have been reported (3-5). However, the correlation of these novel metrics with clinical risk scoring (REVEAL [Registry to Evaluate Early and Long-Term PAH Disease Management]) is less well

LEARNING OBJECTIVES

- To identify long-term IFN- β therapy as a cause of severe PAH.
- To understand the role of serial close monitoring with clinical, imaging (echocardiogram and CMR), and an invasive CPET.
- To understand the treatment goal of achieving a normal exercise-vasodilatory response of pulmonary circulation, including pulmonary vascular distensibility and RV-PA coupling.

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established (6). Here we report a case highlighting the need for a high index of suspicion for a drug-induced cause of a new PAH diagnosis and novel methods to monitor clinical improvement.

HISTORY OF PRESENTATION

A 48-year-old woman was referred to our PAH clinic (University of Wisconsin-Madison, Hospitals and Clinics, Madison, Wisconsin) for evaluation of PAH identified on echocardiogram. She reported rapidly progressive breathlessness with exertion over 6 months, along with occasional exertional light-headedness but no syncope.

PAST MEDICAL HISTORY

She had received a diagnosis of MS at age 40 years, was treated with IFN-β for the past 8 years, and had no MS flares. She reported no other history of PAH risk factors, including thromboembolic disease, connective tissue disease, anorexic drug use, or family history of PAH.

DIFFERENTIAL DIAGNOSIS

Because of the rapid progression of her symptoms, the echocardiogram-based PAH diagnosis, and the absence of risk factors for left-sided heart disease (hypertension, diabetes, coronary artery disease, valvular heart disease, sleep apnea), PAH diagnosis was suspected. Given the absence of risk factors for autoimmune disease or thromboembolic disease, the underlying cause of PAH was presumed to be idiopathic or drug induced (World Health Organization group I).

INVESTIGATIONS

Vital signs included the following: blood pressure (BP), 105/87 mm Hg; heart rate, 93 beats/min; and body mass index, 29.5 kg/m². Oxygen saturation at rest was 98% on room air, and it was de-saturated to 81% on room air with a 6-min walk test (6-min walk distance [6MWD], 266 m). On physical examination, jugular venous pressure was elevated at 16 mm Hg, and a significant RV heave was noted. Cardiac auscultation revealed regular rhythm with a loud P₂ component of second heart sound, and a soft 3/6 holosystolic murmur at the right lower sternal border (exaggerated with inspiration). Brachial pulse volume was reduced, although no leg swelling or hepatosplenomegaly was noticed.

On initial evaluation, her symptoms were consistent with New York Heart Association (NYHA)

functional class III. B-type natriuretic peptide (BNP) was 723 pg/mL (normal <100 pg/mL), and imaging (echocardiogram and cardiac magnetic resonance [CMR]) findings were suggestive of PAH (Figures 1A and 1B and 2A to 2H, Videos 1, 2, 3, and 4). Pulmonary function testing revealed 72% age-predicted diffusion capacity of carbon monoxide (DLCO). Right-sided heart catheterization (RHC) revealed hemodynamic values consistent with severe PAH (Table 1), with no significant response to an inhaled nitric oxide challenge. Other work-ups, including autoimmune serological tests, ventilation-perfusion scan, and noncontrast chest computed tomography, were unremarkable. On the basis of these studies and her unremarkable family history of PAH, she received a diagnosis of World Health Organization group I drug-induced (IFN-β) PAH.

MANAGEMENT

The REVEAL risk score (12, <70% 1-year survival) indicated a high-risk initial presentation (NYHA functional class III; systolic BP <110 mm Hg; heart rate >92 beats/min; 6MWD, 266 m; BNP >180 pg/mL; pericardial effusion on echocardiogram; DLCO, 72%; mean right atrial pressure, 20 mm Hg). IFN-β was suspended, and triple PAH therapy was started (including intravenous treprostinil). Despite her unremarkable family history of PAH, the patient was offered genetic testing, which she decided to consider only if robust clinical improvement was not achieved.

Rapid improvement to NYHA functional class II occurred within a few weeks. On 3 months follow-up, she was taking sildenafil (40 mg 3 times a day), ambrisentan (10 mg daily) and intravenous treprostinil (19 ng/kg/min). All parameters had improved to a low-risk state (Figures 1A and 1B and 2A to 2H, Videos 5 and 6). A cardiopulmonary exercise test (CPET) revealed peak oxygen consumption of 20.2 ml/kg/min (85% predicted), with a peak ratio of minute ventilation to carbon dioxide production of 31 (high risk >32).

Given her significant improvement, intravenous therapy was transitioned to selexipag, 600 μg twice a day, over a 4-week period (choice limited by insurance). Repeat RHC was deferred because of the patient's strong preference. Repeat CMR (6 months after initial diagnosis) revealed an RV ejection fraction of 54% (Figures 2A to 2H, Videos 7 and 8).

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

BP = blood pressure

CMR = cardiac magnetic resonance

CPET = cardiopulmonary exercise test

DLCO = diffusion capacity of carbon monoxide

ET = endothelin

IFN = interferon

MS = multiple sclerosis

NYHA = New York Heart Association

PA = pulmonary arterial

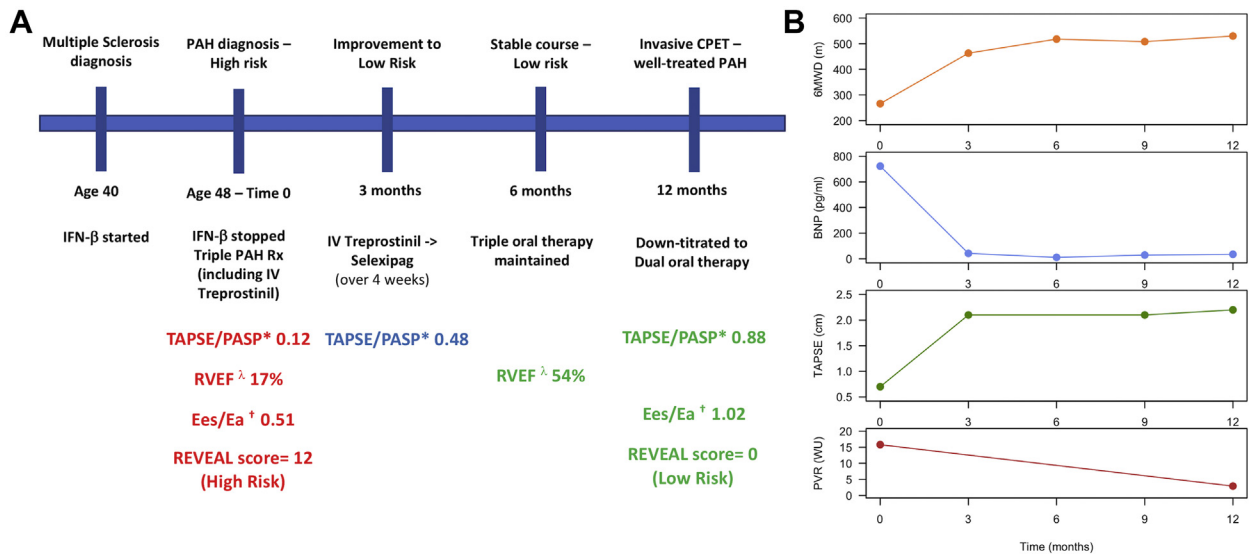
PAH = pulmonary arterial hypertension

RHC = right-sided heart catheterization

RV = right ventricular

6MWD = 6-min walk distance

FIGURE 1 Timeline of Clinical Course With Improvement From High-Risk to Low-Risk State



(A) Overview. (B) Specific values. *Echocardiography-based coupling parameter (ratio of tricuspid annular plane systolic excursion to pulmonary artery systolic pressure [TAPSE/PASP]) (12). ^λCardiac magnetic resonance-based right ventricular ejection fraction (RVEF). [†]Ratio of end-systolic elastance (Ees) to arterial elastance (Ea) (Ees/Ea) as a marker of right ventricular-pulmonary arterial coupling, on the basis of the single-beat method (details in Figure 3). BNP = B-type natriuretic peptide; CPET = cardiopulmonary exercise test; IFN = interferon; IV = intravenous; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; 6MWD = 6-min walk distance.

DISCUSSION

In this case report, we describe the clinical course and management of a female patient with new onset dyspnea and PAH induced by long-term IFN-β therapy. Our case report highlights several important points, including timely identification of PAH in patients receiving long-term IFN-β, guideline-directed PAH therapy, and close follow-up, including exercise testing, which can lead to early clinical stability.

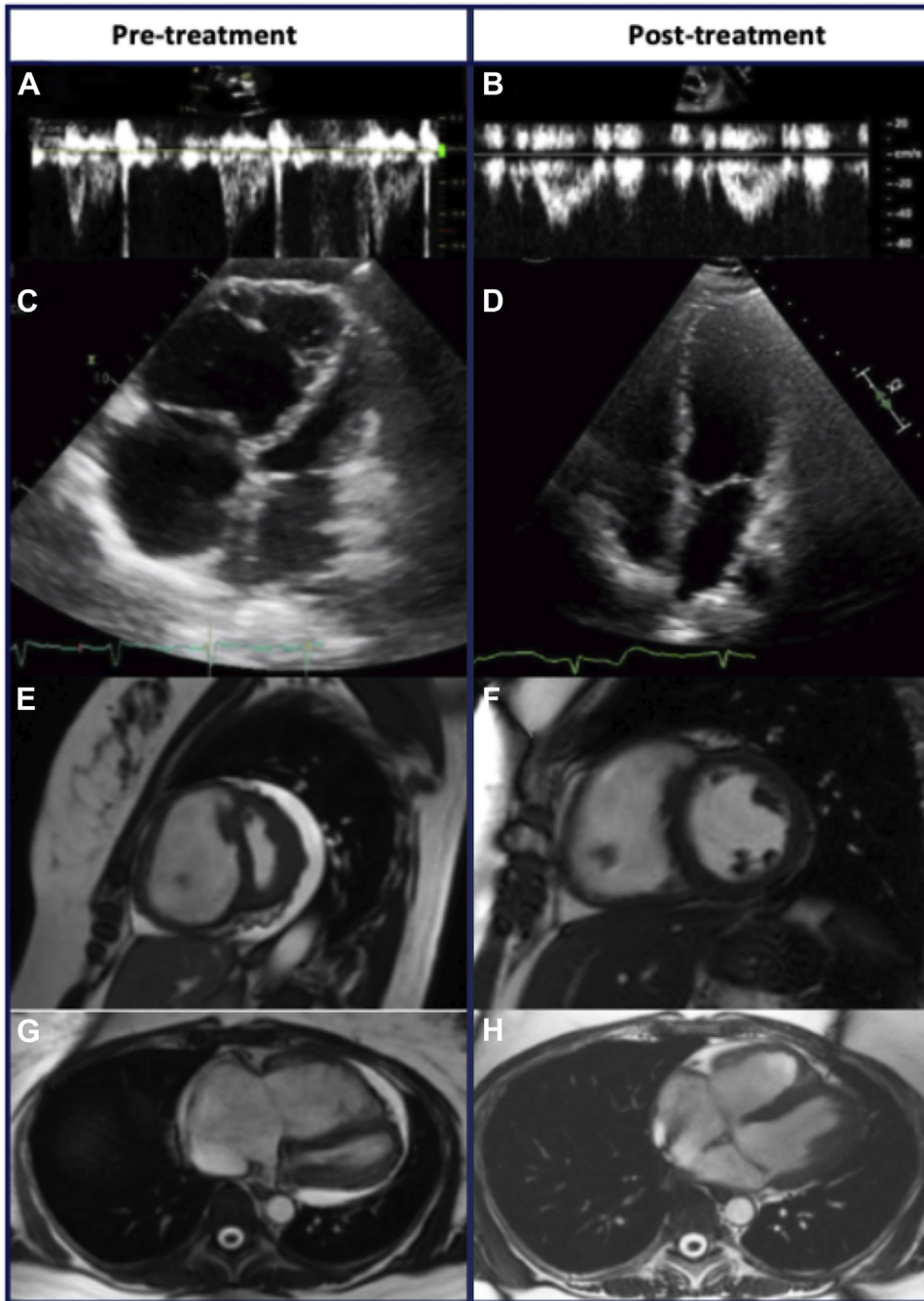
IFNs are cytokines with immunomodulatory, antiviral, and antiproliferative properties. They are classified into type I and type II on the basis of their ability to bind to common receptor types. Type I IFNs include IFN-α and IFN-β, produced by leukocytes and fibroblasts, respectively. Type II IFNs include IFN-γ, produced by T lymphocytes and natural killer cells (7). IFN-α has been used for hepatitis viruses and different malignant diseases, whereas IFN-β is approved for MS (2).

Savale et al. (2,8) reported on 5 patients from a French PAH registry (1998 to 2012) and a summary of a few case reports of patients who developed PAH after 5 to 10 years of IFN-β therapy for MS (total n = 13). In this cohort, histological specimens from 1

patient who underwent lung transplantation revealed typical PAH findings (intimal and medial hypertrophy with adjacent plexiform lesion) (8). The timeline of 8 years between IFN-β initiation and PAH is consistent with a reported range of 5 to 10 years (2). Interestingly, all IFN-β-induced PAH cases were in female patients (total n = 14, including our case). Similar to the strong female preponderance in idiopathic PAH, this disparity is not well understood (1).

The pathophysiological link between type-1 IFNs and PAH has been suggested in animal studies. Badiger et al. (9) reported that IFN-α induced endothelin (ET) 1 in human PA smooth muscle cells, with and without priming with tumor necrosis factor-α. George et al. (10) reported that type 1 IFN receptor knockout mice were protected from effects of hypoxia on the right side of the heart, pulmonary vascular remodeling, and rising ET-1 levels. These studies suggest an important role for type-1 IFN receptor activation leading to increased ET-1 and PAH. As suggested previously, we agree that IFN-β likely leads to PAH in a “susceptible” patient (2). The difference in timeline of different IFNs leading to PAH (5 to 11 months with IFN-α vs. 5 to 10 years with IFN-β) likely reflects the variation in their biological properties (2). However,

FIGURE 2 Improvement of RV Morphology and Function: Pre- and Post-Treatment



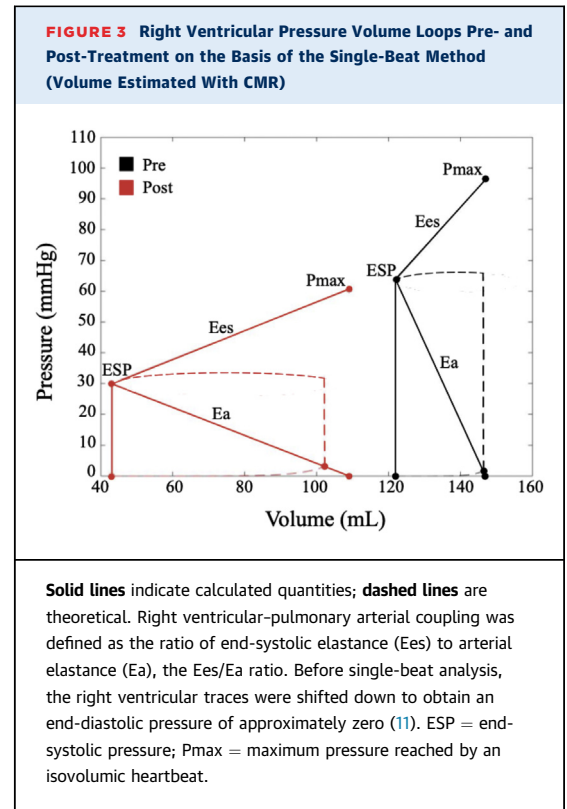
Pre- and post-treatment normalization of **(A and B)** right ventricular (RV) outflow tract Doppler waveform notching pattern (reflects increased right ventricular afterload), **(C and D)** dilated right ventricular apex, **(E and F)** interventricular septal flattening, and **(G and H)** severe right atrial dilation and pericardial effusion.

TABLE 1 Hemodynamics at Initial Diagnosis and 12-Month Follow-Up

	Initial RHC	Post-Treatment	
		RHC: Rest	RHC: Exercise
RA	20	10	14
RV	75/16 edp 26	42/8 edp 14	50/12 edp 17*
PAP	75/43 (55)	42/22 (30)	68/29 (44)
PAWP	14	14	18
Cardiac output	3.58†	5.48	12.58
Cardiac index	1.95†	2.84	6.58
PA sat (%)	56.7%	69.7%	41.1%
SpO ₂ (%)	94%	99%	94%
PVR (woods units)	11.5†	2.9	2.0
PCa (=SV/PP) (ml/mm Hg)	0.9	4.3	2.4
Distensibility (%/mm Hg)			0.903
Ees/Ea	0.51	1.02	
Peak VO ₂ (ml/min)		287	1194
Peak VO ₂ (ml/kg/min)			15.9 (73%‡)
Peak O ₂ pulse (ml/beat)			9.0 (96%‡)
Peak V _E /VCO ₂			28
Peak ETCO ₂ (mm Hg)			39
Delta mPAP/CO (mm Hg/l/min)			2.0
Delta PAWP/CO (mm Hg/l/min)			0.6
PAWL (PAWP/W/kg)			10

*RV tracing obtained almost 10 s after the PA tracing (right atrial tracing obtained in interim, via side-port of the PA catheter). This explains the lower RV systolic pressure, in comparison to PA systolic pressure. †Assumed Fick method (Thermodilution method: cardiac output = 2.60, cardiac index = 1.42, PVR = 15.8). ‡Percentage age-predicted.

CO = cardiac output; Ea = PA elastance; edp = end-diastolic pressure; Ees = end-systolic elastance; ETCO₂ = end-tidal pressure of carbon dioxide; mPAP = mean pulmonary artery pressure; PA = pulmonary artery; PAP = pulmonary artery pressure; PAWL = wedge pressure indexed to workload; PAWP = pulmonary artery wedge pressure; PCa = pulmonary compliance; PP = pulmonary pulse pressure; PVR = pulmonary vascular resistance; RA = right atrial pressure; RHC = right heart catheterization; RV = right ventricular pressure; SpO₂ = systemic oxygen saturation; SV = stroke volume; VE/VCO₂ = minute ventilation to carbon dioxide production; VO₂ = oxygen consumption; WR = work rate.



more studies are needed to identify a direct, causative mechanism.

For disease monitoring during PAH therapies, invasive exercise testing can provide prognostic information about a vasodilatory response of pulmonary circulation with exercise. Pulmonary vascular distensibility quantifies this pulmonary vasodilatory response with exercise, and it is measured as the percentage of increase in pulmonary vessel diameter per mm Hg increase in pressure (normal, 2%/mm Hg; PAH, 0.4%/mm Hg) (4). It represents a sensitive marker of small PA function in different disease states.

Moreover, with invasive hemodynamics, RV-PA coupling can be estimated with a single-beat method (Figure 3) (3,5,11). Theoretically, RV-PA coupling can be estimated during exercise as well as at rest, but signal quality typically suffers. Once RV-PA coupling and distensibility are improved, the PAH therapy can be considered for down-titration with cautious follow-up (Table 1, Figures 1A and 1B). Although our study suggests an association of the

widely used clinical REVEAL risk score with novel metrics of distensibility and RV-PA coupling parameters (Figures 1A and 1B), larger studies are necessary for validation in different PAH phenotypes.

FOLLOW-UP

Over the next 6 months, the patient's clinical course remained stable (Figures 1A and 1B). However, she agreed to undergo repeat RHC because of fatigue symptoms. At approximately 12 months after her initial diagnosis, she underwent an invasive CPET on a semirecumbent bicycle and exercised to 135 W on a 20 W/min protocol, with excellent hemodynamics (Table 1). Her REVEAL risk score was 0 (low-risk: NYHA functional class I; systolic BP \geq 110 mm Hg; heart rate \leq 92 beats/min; 6MWD, 535 m; BNP $<$ 50 pg/mL; no pericardial effusion on echocardiogram; DLCO \geq 80%; mean right atrial pressure, 10 mm Hg). The patient was weaned from selexipag with close follow-up. She continues to follow up with neurology (monitoring with surveillance brain imaging).

CONCLUSIONS

PAH is a rare but life-threatening side effect of IFN- β therapy. Any clinician involved in care of a patient

receiving IFN- β therapy should monitor for early signs of PAH. As in other forms of drug-induced PAH, prompt suspension of the offending drug (IFN- β) and initiation of guideline-directed PAH therapies are essential. Close serial monitoring, with clinical follow-up (every 4 to 6 weeks in the early disease course), imaging follow-up (echocardiogram and CMR within 3 to 6 months), and invasive hemodynamic follow-up with a CPET (within 6 to 12 months), is essential.

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KEY WORDS exercise, pulmonary hypertension, right ventricle

APPENDIX For supplemental videos, please see the online version of this paper.