INTERNAL MEDICINE

□ CASE REPORT □

Interferon Therapy Exacerbated Pulmonary Hypertension in a Patient with Hepatitis C Virus Infection: Pathogenic Interplay among Multiple Risk Factors

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Abstract

Pulmonary arterial hypertension (PAH) is known to develop as a consequence of multiple genetic and/or non-genetic factors. A 27-year-old woman with chronic hepatitis C virus (HCV) infection developed severe PAH after interferon (IFN) therapy. Although most of the reported clinical courses of IFN-induced PAH are poor despite the discontinuation of IFN, the present patient was successfully treated with a triple combination therapy. In this report, we discuss the crosstalk among chronic HCV infection, IFN therapy, autoimmune disorders, and portal hypertension in the pathogenesis and development of PAH.

Key words: portopulmonary hypertension, HCV infection, interferon therapy, up-front combination therapy

(Intern Med 56: 1061-1065, 2017)
(DOI: 10.2169/internalmedicine.56.7822)

Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (PAP) of ≥25 mmHg with right heart catheterization (RHC) (1) and is classified into 5 groups according to the clinical presentation, pathological findings, and hemodynamic characteristics. Drug-induced PH and portal hypertension-associated PH are both categorized into Group 1 PH-pulmonary arterial hypertension (PAH). Multiple genetic and/or non-genetic factors have been reported to contribute to the pathogenesis of PAH (2). Interferon (IFN) is a drug that has been suggested to elevate the risk of developing PAH. Furthermore, chronic inflammation caused by viral infection or autoimmune disease and a female gender are also known risk factors for PAH (3).

In this report, we describe a female case of PAH associated with IFN therapy, portal hypertension, a chronic hepatitis C virus (HCV) infection, and an autoimmune disorder/reaction who presented with multiple triggers, which might have contributed to the development of PAH.

Case Report

A 27-year-old woman was admitted to a general medical center because of worsening dyspnea on exertion in December 2014. She had a history of chronic HCV infection (genotype 1b) and Hashimoto's thyroiditis. Her mother was diagnosed with liver cirrhosis and an HCV infection, so the HCV may have been transmitted vertically from her mother. She was treated with pegylated IFN-α therapy for the HCV infection for 2 months prior to admission. Although the IFN therapy was successful in treating the sustained viral response, she presented with a cough and dyspnea on exertion after the initiation of the IFN therapy. Her symptoms gradually worsened, and she was WHO functional class III on admission.

Her chest radiography revealed dilatation of the pulmonary artery and bilateral pleural effusions (Fig. 1A), and a dominant R wave in lead V1 on electrocardiogram (ECG) indicated right ventricular hypertrophy (Fig. 1B). Doppler echocardiography revealed severe tricuspid regurgitation with a tricuspid regurgitation pressure gradient (TRPG) of

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Received for publication June 8, 2016; Accepted for publication August 21, 2016
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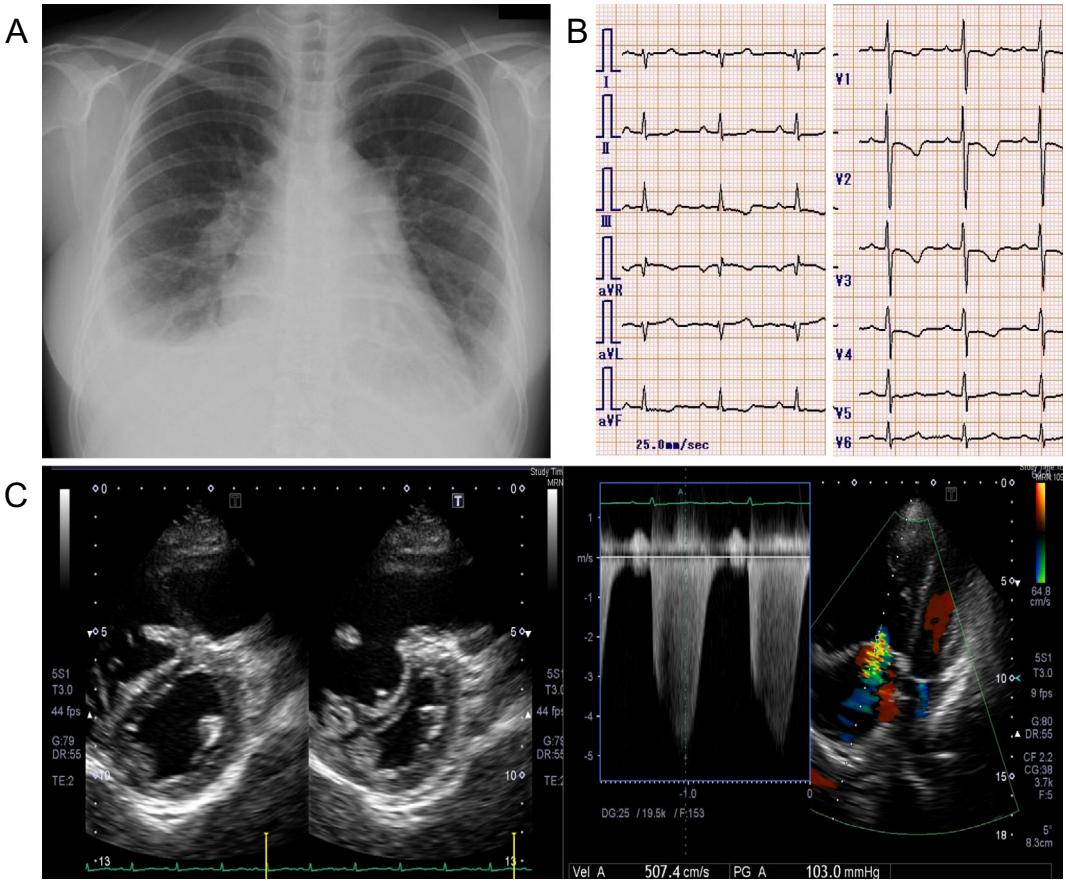

Figure 1. **Chest radiography, electrocardiogram, and echocardiography on admission. A: Chest radiography reveals dilatation of the pulmonary artery, bilateral pleural effusions, and enlargement of the heart. B: Electrocardiogram suggests right ventricular hypertrophy. C: Doppler echocardiography shows flattening of the interventricular septum (left panel) and severe tricuspid regurgitation with a tricuspid regurgitation pressure gradient (TRPG) of >100 mmHg (right panel).**

Table 1. **Summary of Right Heart Catheterization (RHC).**

	1st RHC Dec. 10, 2014	2nd RHC Jan. 29, 2015	3rd RHC Mar. 12, 2015	4th RHC Jul. 14, 2015
HR (bpm)	89	90	73	52
BP (mmHg)	114/61	94/38	99/47	101/58
PAWP (mmHg)	10	16	13	13
RAP (mmHg)	6	11	8	11
PAP (mmHg)	101/44/63	63/23/42	53/14/33	50/19/31
CO (L/min)	4.5	12.7	10.9	6.96
CI (L/min/m^2)	2.9	7.8	6.9	4.3
PVR (Wood units)	11.8	2.3	2.8	2.6

HR: Heart rate, BP: Blood pressure, PAWP: Pulmonary arterial wedge pressure, RAP: Right atrial pressure, PAP: Pulmonary artery pressure, CO: Cardiac output, CI: Cardiac index, PVR: Pulmonary vascular resistance

>100 mmHg and flattening of the interventricular septum, suggesting severe PH (Fig. 1C). RHC on the day of admission (December 10, 2014) confirmed an elevated PAP and pulmonary vascular resistance (PVR) with a normal pulmonary artery wedge pressure (Table 1). IFN-induced PAH was thus suspected, and the IFN therapy was immediately discontinued. A triple combination therapy with epoprostenol (2 ng/kg/min), ambrisentan (5 mg/day), and tadarafil (20 mg/day) was started within 3 days of admission. However, the epoprostenol was discontinued because of a headache. The tadarafil was increased from 20 mg/day to 40 mg/day, and beraprost (120 μg/day) was added instead of epoprostenol.

A second RHC was performed one and a half months af-

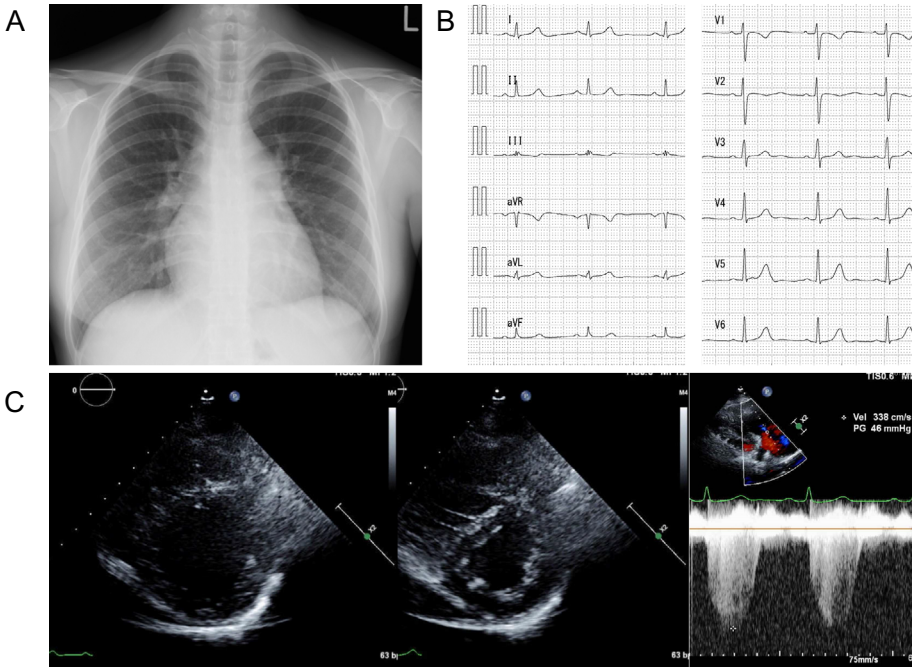

Figure 2. **Chest radiography, electrocardiogram, and echocardiography during the chronic phase (7 months after admission). A: Chest radiography shows mild pulmonary artery dilatation without any pleural effusion. B: Electrocardiogram shows no sign of right ventricular hypertrophy. C: Doppler echocardiography shows mild flattening of the interventricular septum and mild tricuspid regurgitation with a tricuspid regurgitation pressure gradient (TRPG) of 46 mmHg.**

ter the discontinuation of the IFN and starting the administration of pulmonary vasodilators, revealing a decreased PAP (from 101/44/63 to 63/24/42 mmHg) and PVR (from 11.8 to 2.3 Wood units) and an increased cardiac output (CO) (from 4.5 to 12.7 L/min). Her respiratory condition gradually improved, although her PAP was still high.

Considering her medical history and clinical course, IFN-induced PAH was suspected. Serological tests were positive for anti-ds-DNA antibody, which suggested the concomitant involvement of connective tissue disease-associated PAH. She was therefore transferred to our hospital for further assessment of PAH in March 2015. On a physical examination, a Levine 3/6 systolic murmur was detected at the 5th intercostal space by the right sternal border. An abdominal examination revealed hepatosplenomegaly. A peripheral examination revealed no pedal edema. She had no characteristic findings of connective tissue diseases such as a skin rash on the face, joint pain, a low-grade fever, or Raynaud's phenomenon. Furthermore, the anti-ds-DNA antibodies turned negative (Table 2), suggesting transient immunomodulation by the IFN.

Abdominal ultrasonography and computed tomography (CT) suggested chronic liver disease with splenomegaly. A liver biopsy was performed for further assessment of the chronic liver disease, and F4 stage fibrosis (liver cirrhosis) was revealed. A ventilation/perfusion lung scan showed no significant mismatch. High-resolution CT did not show any signs of interstitial lung disease or emphysema.

A decrease in the PAP (53/14/33 mmHg) was observed during the third RHC (Table 1). The oximetry run during the RHC did not suggest left-to-right intracardiac shunts. An elevated PAP and high CO indicated portopulmonary hypertension (POPH). The IFN might have triggered an acute worsening of POPH. A fourth RHC performed 7 months after the interruption of the IFN therapy indicated further hemodynamic improvement as follows: PAP 50/19/31 mmHg, CO 6.96 L/min, CI 3.63 L/min/m^2, and PVR 2.6 Wood units (Table 1). The results of chest radiography, ECG, and echocardiography also suggested an improvement in her PH (Fig. 2). She was stable in WHO functional class II with combination therapy of ambrisentan (5 mg/day), tadarafil (40 mg/day), and beraprost (120 μg/day).

Discussion

In this report, we described a woman with vertically transmitted chronic HCV infection and autoimmune thyroiditis in whom IFN therapy induced a worsening of POPH. This case highlights the contribution of multiple risk factors in triggering and developing PH (Fig. 3).

A clinical classification of PH was established by categorizing PH into 5 groups, which share similar pathological and hemodynamic characteristics (3, 4). Drug- and toxin-induced PH and POPH are both categorized into Group 1 (i.e. PAH). A number of drugs and toxins have been identified as risk factors for the development of PAH. They are categorized according to the strength of the available evidence to this end as "definite", "likely", and "possible". IFN is listed as a "possible" risk factor (4).

IFN has growth regulatory properties and a wide variety

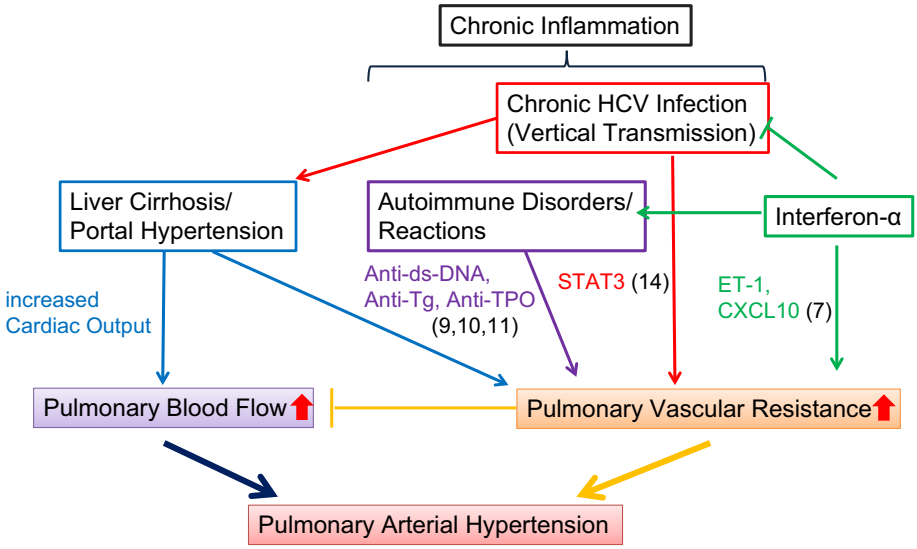

Figure 3. **Pathogenic interplay among multiple risk factors for PAH. A schematic representation of the pathogenic interplay among chronic HCV infection, IFN, liver cirrhosis/portal hypertension, and autoimmune disorders/reactions for the development and worsening of pulmonary arterial hypertension. HCV: Hepatitis C virus, IFN: interferon, Anti-ds-DNA: Anti-double strand-deoxyribonucleic acid, Anti-Tg: Anti-thyroglobulin, Anti-TPO: Anti-thyroperoxidase, ET-1: Endothelin-1, CXCL10: Chemokine ligand 10**

Table 2. **Laboratory Findings on Mar. 12, 2015.**

WBC	3,289 /μL	TP	5.3 g/dL	Tg Ab	211 IU/mL
Hb	9.8 g/dL	Alb	4.0 g/dL	TPO Ab	7.1 IU/mL
Hct	30.1 %	CK	30 IU/L	ds-DNA Ab	<2 IU/mL
Plt	17.5×10^3/μL	KL-6	160 IU/L	ACL-β2GPI	<8 IU/mL
		CRP	0.07 mg/dL	RF	<10 IU/mL
Na	139 mEq/L				
K	3.8 mEq/L	PT-INR	1.20	HBs-Ag	(-)
Cl	106 mEq/L	APTT	34.5 sec	HBs-Ab	(-)
BUN	18.7 mg/dL	Fibrinogen	202 mg/dL	HCV-Ab	(+)
Cre	0.97 mg/dL	FDP	1.6 μg/mL	HCV-RNA	(-)
eGFR	70 mL/min	D-dimer	0.27 μg/mL	HIV	(-)
T-Bil	0.9 mg/dL	Protein S	78 %		
AST	25 IU/L	Protein C	60 %	*Blood gas analysis (room air)*	
ALT	7 IU/L			pH	7.467
LDH	190 IU/L	BNP	71.7 pg/mL	pCO_2	35.0 mmHg
ALP	184 IU/L	TSH	5.11 μIU/mL	pO_2	88 mmHg
γ-GTP	43 IU/L	FT4	0.8 ng/dL	HCO_3^-	24.6 mEq/L
UA	3.0 mg/dL	FT3	2.8 pg/mL	BE	0.8 mmol/dL

of immunomodulatory activities and exerts antiviral activity, inhibitory effects on angiogenesis, a regulatory effect on cell differentiation. There are several case reports that have suggested a pathogenic role of IFN in the development of PAH (5, 6). George et al. reported a possible molecular mechanism by which IFN may mediate the development of PAH via activation of interferon γ inducible protein 10 (IP 10; CXCL10) and endothelin-1 (ET-1) (7). However, most patients diagnosed with IFN-induced PAH in a French registry and some case reports have described the association of other risk factors with PAH, such as portal hypertension and/or human immunodeficiency virus infection (8). In this case, the patient had chronic liver disease (liver cirrhosis) and Hashimoto's thyroiditis, both of which (9-11) are known to be associated with PAH. IFN may therefore have acted as the trigger for the development of PAH and/or worsening of asymptomatic PAH in our patient.

No treatment strategy for IFN-induced PAH has yet been established, due to a lack of evidence. The prognosis of IFN-induced PAH is usually poor, despite the discontinuation of IFN and administration of pulmonary vasodilators (8). A delay in the diagnosis and administration of PAH-specific medications may be associated with a worse outcome. In this case, the discontinuation of the IFN and

early PAH-specific combination therapy may account for the successful treatment of IFN-induced PAH.

POPH has been reported in approximately 6-9% of patients with advanced liver disease, and a higher incidence is shown in patients with HCV-related cirrhosis (12). In addition, HIV and HCV coinfections are known to increase the risk of PAH compared with HIV monoinfection. Several experimental studies have also demonstrated that HCV activates the STAT3 axis, which plays an important role in the pathogenesis of PAH (13, 14).

In conclusions, the vertically transmitted longstanding chronic HCV infection itself might have been associated with the development of asymptomatic PAH before IFN therapy in this case. Unfortunately, echocardiography was not performed before the IFN therapy. The present case had multiple PAH risk factors-namely liver cirrhosis, a chronic HCV infection, Hashimoto's thyroiditis, and female gender. We postulate that the IFN may have triggered the acute worsening of PAH via the activation of ET-1 and CXCL 10 and modulation of the immune response. All of these risk factors and triggers may have contributed to the development of PAH by interacting with each other (Fig. 3). Clinicians should be alerted to these potential risk factors for PAH exacerbation and should perform echocardiography for PH screening before and after the administration of IFN therapy.

The authors state that they have no Conflict of Interest (COI).

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