PH GRAND ROUNDS

Interferon-Associated Pulmonary Arterial Hypertension

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Presentation: A woman aged 54 years with multiple sclerosis (MS), chronic obstructive pulmonary disease (COPD), and hypertension presented with progressive exertional dyspnea and fatigue noted over 8 months. Multiple sclerosis was diagnosed 15 years earlier and treated with subcutaneous interferon-β for 10 years with subjective and clinical benefits. She described gradual fatigue and breathlessness with walking, climbing stairs, and performing activities of daily living but denied exertional chest pain, syncope, or lower extremity edema. She attributed her symptoms to worsening MS, however, her treating neurologist did not identify clinical or magnetic resonance imaging (MRI) indicative of worsening progressive MS. Because she was a daily smoker, her exertional dyspnea was attributed to COPD, and pulmonary function testing confirmed a diagnosis of airflow limitation with a decreased diffusion capacity; results were FEV1: 2.22 L (85% predicted), FVC: 3.44 L, FEV1/FVC: 0.65, DLCO: 9.0 mL/min/mm Hg. In addition, an arterial blood gas (FiO_2: 0.21) revealed 7.41/39/80. Yet, despite use of nebulized albuterol every 6 hours, her exertional dyspnea was not relieved, and she was referred for further assessment of exertional dyspnea.

Assessment: At the initial visit, she reported more breathlessness with mild physical activity and felt dizzy climbing stairs over the previous 12 months. She described fatigue and frustration regarding her declining physical activity and was concerned because she had noted improvements in fatigue and walking for years after being started on interferon. She smoked one-half pack of cigarettes per day to curtail her anxiety. She denied prior pulmonary emboli, deep vein thrombosis, illicit drug use, chronic liver disease, or family history of pulmonary hypertension (PH). Medications included aspirin, baclofen, gabapentin, atorvastatin, omeprazole, escitalopram, mirtazapine, and interferon β-1B (250 mcg subcutaneously every other day). Physical examination findings revealed a thin woman with blood pressure 124/80 mm Hg, pulse 95 min^{-1}, respirations 20 min^{-1}, SpO_2 99%, weight 59 kg, and BMI 22 kg/m^2. Pertinent findings included jugular venous distention, cardiac auscultation demonstrated 3/6 systolic murmur over left lower sternal border, and absent lower extremity edema. Transthoracic echocardiography was performed that revealed an left ventricular ejection fraction (LVEF) 50% to 55%, mild mitral regurgitation, right ventricular dilation, right ventricular systolic pressure of 120-125 mm Hg, and no pericardial effusion. A ventilation perfusion scan revealed subsegmental filling defects with delayed washout chest consistent with airflow limitation. Computer axial tomography with angiography of the chest demonstrated no pulmonary vascular filling defects, right ventricular enlargement, and upper lobe centrilobular emphysema. Additional studies revealed negative ANA, HBV, HCV, and HIV serology. During a 6-minute walk testing, she ambulated 900 feet without exercise desaturation. Right heart catheterization was performed that revealed a hemodynamic profile consistent with precapillary PH (Table 1).

Management: After review of her clinical information, the cause of pulmonary arterial hypertension (PAH) was attributed to interferon-β therapy. A discussion with the patient, her family, and neurology and PH consultants led to discontinuation of interferon, which was replaced with dimethyl fumarate for treatment of MS. Her functional 3 status and clinical findings led to initiation with sildenafil 20 mg tid and ambrisentan 5 mg/day with subsequent dose increase to 10 mg/day.

Eight weeks after being initiated on PAH-specific therapy, she reported improved physical endurance and resolution of episodes of exertional dizziness.

Key Words—interferon, multiple sclerosis, pulmonary arterial hypertension
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Table 1. Baseline and 1-year hemodynamic profile

	MAP	RA	RV	PAP	PCWP	CO	CI	6-minute walk
Initial	93	12	103/4	103/46 (68)	13	2.98	1.8	900 ft
12 month	90	12	63/9	70/33 (47)	10	5.5	3.3	1140 ft

She indicated walking with her granddaughter during Halloween without having to stop and hosted Thanksgiving dinner at her home, a tradition she had previously given up due to declining health. Six-minute walk distance increased to 1000 feet. Twelve months after initiation of combined PAH-specific therapy, a right heart catheterization and 6-minute walk confirmed improvement in hemodynamics and exercise tolerance (Table 1).

Discussion: Pulmonary arterial hypertension associated with medications has been recognized since the 1960s, when aminorex was identified as a causative agent.[1] Over the ensuing years, the number of drugs associated with PAH has increased and recent reviews highlight the drugs and toxins associated with PAH.[2,3] A partial set of medications associated with PAH include anorexic agents aminorex, fenfluramine, and benfluorex; tyrosine kinase inhibitor dasatinib; chemotherapy mitomycin, and interferon. Moreover, drugs implicated with the development of PAH account for 10.5% of subjects enrolled in the REVEAL Registry.[4]

For years, interferon has been implicated as a drug associated with development of PAH. The initial report concerned a patient with renal cell carcinoma treated with interferon-α that developed PH followed by resolution after drug discontinuation.[5] Subsequently, other reports described patients with hematological disorders and malignancies treated with interferon therapy that resulted in PAH.[6,7] As the indications for interferon therapy expanded to include chronic hepatitis and multiple sclerosis, there followed a series of case reports describing PAH following exposure to interferon-α and interferon-β.[8-12] An early description involved a 59-year-old patient prescribed interferon-β therapy for treatment of MS with progressive decline in physical activities after 1 year and eventually underwent a right heart catheterization that confirmed the diagnosis of PAH. Notably, after cessation of interferon and administration of sildenafil, the patient's symptoms improved along with echocardiography findings.[13]

Subsequently, a retrospective case series from the French Registry described a cohort of patients diagnosed with PAH that had been previously treated with interferon.[14] Forty-eight patients with chronic liver disease and evidence of portal hypertension and 1 patient with chronic myelogenous leukemia were prescribed interferon-α for a median of 7.7 months with a predominance of men (69%) developing right heart dysfunction. These patients with chronic liver disease underwent right heart catheterization with the following findings: right atrial pressure 7 ± 5 mm Hg; mean pulmonary artery pressure 46 ± 10 mm Hg; PCWP 8 ± 3 mm Hg; cardiac output 5.5 ± 1.5 L/min; and pulmonary vascular resistance 7.7 ± 3.6 Wood units. In this cohort who were prescribed interferon-α, 16 patients were known to have PAH prior to interferon treatment and 27 patients (56%) were coinfected with HIV. In contrast, 5 female patients with MS received interferon-β for a median of 80 months, and aside from the presence of an atrial septal defect in 1 patient, no risk factors for PAH were identified among this cohort. Right heart catheterization was performed in this group that confirmed precapillary PH as noted by the following: mean pulmonary artery pressure 61 ± 9 mm Hg; cardiac output 4.5 ± 2.9 L/min; and pulmonary vascular resistance 17.1 ± 15.4 Wood units. The outcomes for 5 patients with MS treated with interferon-β included 2 deaths related to PAH. In those patients treated with interferon-α, 8 were prescribed PAH-specific therapy. Of note, interferon was discontinued in another 13 patients treated with interferon-α, which resulted in clinical and hemodynamic improvements without the need for additional therapy.[14] Another interesting feature concerns the histopathology of interferon-β–induced PAH that appears to be similar to other causes of precapillary PH, namely intimal proliferation, medial hypertrophy, and plexiform lesions.[15] Recently, Papani et al conducted an epidemiologic study that examined administrative claims data in a US population of commercially insured patients to determine the frequency of PAH after initiation of interferon therapy.[16] From April 2001 to December 2012, the investigators identified 20,113 adults who received interferon for hepatitis C or MS. Seventy-one patients were diagnosed with PH with a mean follow-up time of 52.2 ± 33.5 months. Among those patients who developed PH, 7 were treated with PAH-specific medications; these 7 patients were considered to represent the interferon-induced PAH group. Considering the published estimates for the incidence of PAH are 1.1 to 7.6 per million adults per year,[16] the investigators should have identified less than 1 patient among their study cohort, and yet they identified 7 patients with PAH. This suggests that the risk of developing PAH in patients with hepatitis C or MS treated with interferon was 6-fold higher than in the general population.

Interferon-α and interferon-β are prescribed to treat chronic myelogenous leukemia, hairy cell leukemia, melanoma, renal cell carcinoma, AIDS-related Kaposi's sarcoma, chronic hepatitis C, and MS.[18,19] They are glycoproteins with antiviral, immunomodulatory, and antitumor action produced by the host in response to exposure to pathogens and tumor cells. Interferons have been categorized to 3 distinct types; interferon-α, interferon-β, and interferon-γ. While the mechanism behind interferon therapy and development of PAH remains uncertain, various investigators have examined this issue. In a minority of patients with hepatitis C treated for 6 months with interferon-α, elevated serum endothelin levels were reported, and

this was related to interferon administration.[20] Although none of these patients developed PH, the follow-up time was not long enough. Another group set out to examine the role of interferon 1 pathways in the activation of PAH in patients with scleroderma using in vitro and in vivo techniques.[21] The investigators reported type 1 interferon induced release of interferon gamma inducible protein 10 (IP10), implicated in lung inflammation, and endothelin-1 from human pulmonary artery smooth muscle cells. Notably, patients with scleroderma and PAH had higher endothelin-1 and IP10 serum levels compared with scleroderma patients without PAH. In addition, examination of lung sections obtained from patients with scleroderma and PAH demonstrated increased interferon receptor expression in pulmonary vasculature scleroderma patients with PAH. The investigators concluded that interferon stimulated genes that included IP10 and endothelin via the interferon receptor. Collectively, these clinical case series and epidemiologic studies provide data regarding association of interferon exposure and development of PAH. Furthermore, scientific mechanistic studies have been reported to elucidate the mechanisms regarding the relationship between dysregulated innate immunity and pulmonary vascular pathology.

Teaching Points

1. Interferon-α and interferon-β are associated with development of PAH.
2. Patients with chronic conditions treated with interferon therapy may develop PAH in an insidious manner.
3. PAH associated with interferon-α and interferon-β exposure may occur with drug exposure of 5 to 120 months.
4. The hemodynamic profile and histopathology of interferon-associated PAH is similar to other forms of precapillary PH.
5. Resolution of interferon-associated PAH may occur after drug discontinuation.
6. PAH-specific combination therapy with sildenafil 20 mg tid and ambrisentan 10 mg/day can improve exercise tolerance and hemodynamics in patients with interferon-associated PAH.

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