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Connective Tissue Disease Presenting With Signs and Symptoms of Pulmonary Hypertension in Children

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Abstract

Our case series describes three children who were initially diagnosed as having severe pulmonary arterial hypertension (PAH) and subsequently found to be positive for specific autoantibodies suggestive of an underlying autoimmune process. The signs and symptoms of PAH are subtle and may be part of the initial presentation of childhood connective tissue disease (CTD). Evaluation for connective tissue disease in the newly diagnosed pulmonary hypertension (PH) patient is important because early diagnosis of PH as well as CTD is crucial in the successful management of these complex patients. Ongoing monitoring for CTD in patients with severe PAH is warranted.

Keywords

Pulmonary arterial hypertension; Autoantibody; Pulmonary vasodilator therapies; Antinuclear antibody; Connective tissue disease; Children

Introduction

Signs and symptoms at initial presentation of many pediatric disorders may be subtle. The time from the onset of symptoms to diagnosis of pulmonary hypertension (PH) is usually 1–2 years because children initially present with dyspnea on exertion, which may be initially diagnosed as asthma. Similarly, children with connective tissue diseases (CTDs), such as systemic sclerosis, mixed CTD, and systemic lupus erythematosus (SLE), may present with nonspecific symptoms, which often delays the correct diagnosis. In addition, autoimmune diseases can evolve with time, so there may be a delay until a patient meets specific diagnostic criteria to confirm the diagnosis.

Pulmonary arterial hypertension (PAH) complicates the course of some patients with CTD. Furthermore, the recent World Health Organization classification recognizes PAH associated with CTD in Group 1 PAH and CTD as one of the most common forms of PAH in adults. It has been estimated that almost 30% of adult cases of PAH are associated with CTD, including 10% to 15% cases with systemic sclerosis [6]. Among these patients, PAH is often multifactorial, including pulmonary fibrosis-related CTD and thrombosis associated with vasculitis and/or thrombophilia. PAH associated with CTD is also a major risk factor for death in these patients. Recently, various pulmonary vasodilator therapies have improved the prognosis for patients with PAH associated with CTD. Previous studies have been shown that epoprostenol (PGI₂) increased exercise capacity compared with conventional

therapy in patients with PAH associated with systemic sclerosis [1] and improved hemodynamics and exercise capacity in patients with SLE [8].

Case Reports

Case No. 1

Case no. 1 is a 14-year-old Hispanic girl who was healthy until 1 year before presentation, when she developed exercise intolerance and frequent syncopal events. There was no family history of PH, sudden death, thromboembolic disorders, chronic lung disease, or CTD. Her initial echocardiogram demonstrated severe PAH, with estimated right-ventricle (RV) systolic pressure 96 mm Hg greater than right atrial pressure, a dilated RV with diminished systolic function, and a compressed left ventricle from the enlarged RV. Pulmonary function tests found no evidence of obstructive or restrictive disease. Rheumatologic screening tests showed a positive lupus anticoagulant (Russell Viper Venom Test [RVVT] ratio 1.5 [normal<1.2]) and a positive antinuclear antibody (ANA) titer of 1:320 with a speckled pattern, but all other serum autoantibodies were negative, including double-stranded DNA (dsDNA), Smith, ribonucleoprotein (RNP), Sjogren's-specific antibody A (SSA), Sjogren's-specific antibody B), and rheumatoid factor. Her serum complement levels, including C3 and C4, were normal. Due to marked hemodynamic instability, she was started on low-dose PGI₂ and inhaled nitric oxide (iNO). At initial cardiac catheterization, slow weaning of iNO resulted in a PH crisis with a decrease in systemic blood pressure and a 2-fold increase in mean pulmonary arterial pressure (mPAP). Due to her severe and recurrent syncope and association with severe PAH, intravenous PGI₂ was initiated. After starting PGI₂ therapy, her hemodynamics dramatically improved. Her estimated RV systolic pressure was 56 mm Hg greater than right atrial pressure on echocardiography, and follow-up cardiac catheterization showed mPAP 26 mm Hg and pulmonary vascular resistance index (PVRI) 1.42 Units × m² on 20 ppm iNO and PGI₂. However, she continued to have dizziness and near syncopal episodes. At 2 years after her PAH was diagnosed, repeat cardiac catheterization showed that her PAH had not deteriorated because mPAP was 21 mm Hg. However, she had near syncope and then underwent an atrial septostomy; sildenafil therapy was added. Her symptoms resolved, and therefore she was weaned off PGI₂ infusion therapy without any rebound effects. She continued sildenafil mono-therapy, and Doppler echocardiography showed mild to moderate increase of systolic RV pressure (58 mm Hg greater than right atrial pressure). During sequential laboratory examinations 2 years after diagnosis, she developed strongly positive anti-SSA, anti-RNP, anti-Sm, and anti-DNA antibodies as well as low complement levels. Other antibodies, such as anti-Jo 1, antiScl-70, and antineutrophil cytoplasmic antibodies, remained negative. Three years after diagnosis, she had intermittent joint pain with difficulty walking. She also complained of swelling of her fingers, ankles, and feet. At that point, her clinical picture was consistent with a lupus-like illness because she met 3 out of 11 criteria for SLE; thus, we initiated treatment with oral glucocorticoids. Her symptoms improved with methylprednisolone. In addition, she was maintained on warfarin due to her persistently positive antiphospholipid antibodies. She continues to have positive anti-SSA, anti-RNP, anti-Sm, anti-DNA antibodies, but she has not developed any new signs or symptoms of SLE or any other underlying CTD at 7 years after her initial diagnosis of PAH.

Case No. 2

Case no. 2 presented at the age of 10 years. He is a Hispanic boy who is one of identical twins; his brother is healthy, and they both had twin-to-twin transfusion syndrome. His mother and grandfather have a history of idiopathic thrombocytopenia (ITP) that required splenectomy. In addition, his maternal grandmother had Raynaud's phenomenon. The patient's initial symptoms included daily vomiting, weight loss, and Raynaud's phenomenon.

Due to complaints of easy fatigability with shortness of breath and syncope, an echocardiogram was performed, and he was found to have severe PAH 2 months after the onset of his symptoms. The echocardiogram demonstrated moderate to severe tricuspid insufficiency with an estimated RV pressure at least 80 mm Hg greater than right atrial pressure. Initial cardiac catheterization showed mPAP 54 mm Hg and PVRI $16.4 \text{ Units} \times \text{m}^2$ on room air. He also underwent chest computed tomography (CT), which was normal without any evidence of interstitial lung disease. Despite his normal CT scan, his pulmonary function tests (PFTs) were abnormal, suggestive of restrictive lung disease because his forced vital capacity (FVC) was 1.42 L (61% of predicted) with forced expiratory volume in 1 s (FEV₁) 1.35 L (65% of predicted). Ventilation/perfusion lung scan showed no evidence of pulmonary thromboemboli. ANA titer was markedly increased (1:2560) with a speckled pattern. Dilute RVT was positive for lupus anticoagulant. Anti-dsDNA, anti-Smith, anti-RNP, anti-SS-A, anti-SS-B, and anti-SCL-70 were negative, and complement levels were normal at onset. He was diagnosed with a scleroderma variant given his severe PAH, positive lupus anticoagulant, Raynaud's phenomenon, and sclerodactyly on examination. He was started on PGI₂ infusion due to his severe PAH with heart failure. Bosentan therapy was added due to lack of improvement and resulted in increased exercise capacity. However, cardiac catheterization showed continued severe PAH with mPAP 58 mm Hg and PVRI $15.7 \text{ Units} \times \text{m}^2$ at 1-year follow-up. Despite aggressive medical therapy for PAH, he had presyncope and evidence of right heart failure and therefore underwent atrial septostomy, and sildenafil therapy was added at 2 years after diagnosis. Overall, he improved and attended high school. One year after presentation, he developed high titer-positive anti-RNP and anti-SSA antibodies and decreased complement levels. He received treatment with cyclophosphamide and continued this therapy for 3 years. For 9 years after diagnosis, he was maintained on prednisone, 10 mg daily, with no progression of signs or symptoms of CTD. However, when he developed parainfluenza 7 years after presentation, his platelet count decreased to $<30,000$, and he was treated with increased steroids and IVIG for presumed ITP considering his familial history and temporary thrombocytopenia after a viral infection. Since that time, he has received treatment with rituximab for recurrent thrombocytopenia.

Case No. 3

Case no. 3 is an 8-year-old Hispanic boy who presented with exercise intolerance and shortness of breath. At the same time, he developed muscle pain in his upper arm and thighs. He also complained of pain and swelling of his hands at the proximal interphalangeal and metacarpophalangeal joints. His mother noted that his hands and toes became cold and often pale, alternating with a purple color, particularly with cold exposure, consistent with Raynaud's phenomenon. His maternal great-aunt was diagnosed with lupus. There are no other known family members with any autoimmune disease or PH. Due to shortness of breath, an echocardiogram was performed and demonstrated a moderate pericardial effusion and evidence of PAH, with an estimated RV systolic pressure 70 mm Hg greater than right atrial pressure. ANA was positive with a titer $>1-1280$ with a speckled pattern. RNP antibody and rheumatoid factor were also positive. Other antibodies, including anti-SSA, anti-Smith, and anti-DNA antibodies, were all negative. Creatine phosphokinase was increased at 1218 IU/L with increased creatine kinase-MB 25.9 ng/mL. Chest CT showed a moderate pericardial effusion with small bilateral pleural effusions. There was no evidence of interstitial lung disease by chest CT, but he was diagnosed with restrictive lung disease based on his PFTs because his FVC was 1.13 L (66% of predicted) and FEV₁ was 1.05 L (70% of predicted). His pericardial effusion spontaneously resolved, but PFTs remained abnormal. Cardiopulmonary exercise testing showed peak oxygen consumption 26.5 mL/kg/min (56% of predicted VO₂ max) and ventilatory equivalent for carbon dioxide ratio of 39. He was diagnosed with mixed CTD with a positive RNP antibody, Raynaud's phenomenon,

and PAH. He began bosentan and immunosuppressive therapy with methotrexate and prednisone. His symptoms improved, and his joint pain nearly resolved. Repeat echocardiography and catheterization 5 years after diagnosis demonstrated hemodynamic parameters that were almost normal. Because his PAH normalized during 5 years, he was switched from bosentan to calcium channel-blocker therapy. His most recent laboratory examination showed the presence of high-titer anti-RNP and anti-Sm antibodies. He subsequently developed thrombotic thrombocytopenic purpura as confirmed by deficiency of the von Willebrand factor-cleaving metalloprotease ADAMTS13, and his methotrexate was changed to mycophenolate.

Discussion

Both CTD and PAH can be difficult diagnoses to make in children. The presentation of each may be delayed due to subtle symptoms. The time from onset of symptoms to correct diagnosis of PAH is usually >1 year. Similarly, CTD can be difficult to diagnose in children because clinical manifestations are nonspecific and may include fever, rash, and joint pain. In patients with CTD, PAH is usually diagnosed after many years. In this series, we present three cases in which the initial presentation of CTD was complicated by or presented with PAH. Table 1 lists clinical information for the three patients. As listed in Table 2, at onset two of three patients had minor symptoms of CTD, such as Raynaud's phenomenon and muscle pain. All patients had signs of PH, including shortness of breath, exercise intolerance, and syncope.

The prevalence of PAH in patients with systemic sclerosis in adults has been reported between 7 and 12% as evaluated by echocardiography and right heart catheterization [4]. In SLE [12] and mixed CTD [2, 5], the prevalence of PAH remains unknown. Patients having PAH associated with CTD generally have a worse prognosis than those with idiopathic PAH (IPAH) [3]. Treatment with PAH-specific therapy has improved the prognosis for patients having PAH associated with CTD [1, 8, 9]. Two of three patients in our study were treated with combination therapy for PAH because of deterioration on monotherapy. Therefore, it is important to diagnose and treat these patients at an early stage.

Recent human studies have shown that combining vasodilator drugs may have beneficial effects. Our cases also suggest that combination therapy with different mechanisms could be effective. Adult patients with PAH and CTD have less severe hemodynamic abnormalities than patients with IPAH, but the prognosis of patients having PAH associated with CTD, especially in SSc, is markedly worse than IPAH [10]. Among patients with CTD, PAH is usually progressive, and RV hypertrophy and failure leads to death.

Our patients had high levels of autoantibodies, particularly anti-RNP antibodies. Two patients also had evidence of antiphospholipid antibodies. However, there was no evidence of thrombus or thromboembolic events in our patients. In patients with CTD, autoantibodies are a strong predictor of interstitial lung disease. Likewise, anti-RNP antibody is associated with an increased risk of pulmonary disease, such as severe interstitial fibrosis, in adults [11]. In our patients, severe PAH was noted, but no lung fibrosis was observed. We speculate that autoantibodies may have affected the small pulmonary arteries in patients unaccompanied by lung fibrosis, and combinations of more advanced immunosuppressive therapies may be effective in preventing the progression of PAH.

Two of our three patients with severe PAH had positive autoantibodies without typical symptoms of CTD at presentation. Our observations highlight the importance of a complete evaluation for all causes of PAH on initial presentation and at regular intervals after diagnosis. Many of these patients require aggressive PAH therapy. As listed in Table 2,

cases no. 1 and 2 were severely impaired functionally and tended not to respond well to therapy. Others, such as case no. 3, have remained stable for 7 years. In addition, it is difficult to standardize treatments based on the variability of manifestations and response to specific medications; therefore, the treatment approach should be flexible and individualized.

Interestingly, in our case series, all three patients are Hispanic. In a recent report, Nashid et al. demonstrated a racial difference, including African-American, Hispanic, and white European, in patients with SSc [7]. They described that Hispanic patients may present with more severe disease than African-American or white patients. Genetic factors may be associated with such differences in the ethnic groups. These findings suggest that physicians need to be even more vigilant in Hispanic patients.

In conclusion, the signs and symptoms of PH may be part of the initial presentation of childhood CTD. Evaluation for CTD in the newly diagnosed PAH patient is important because early diagnosis of PAH as well as CTD is crucial in the successful management of these patients. Ongoing monitoring for CTD in the patients with severe PAH is warranted.

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Table 1

Patient profile

Characteristics	Case no. 1	Case no. 2	Case no. 3
Gender	F	M	M
Race	Hispanic	Hispanic	Hispanic
Age at diagnosis (year-old)	14	10	8
Vasodilator therapies	Sildenafil	Tadalafil	Amlodipine
	Amlodipine	Ambrisentan	
	PGI ₂	PGI ₂	
Other therapies	Diuretics	Diuretics	Methotrexate
	Warfarin	Prednisone	Prednisone
	Methylprednisolone	Atrial septostomy	
	Atrial septostomy		
Follow-up period (year-old)	7	9	7
ANA titer at diagnosis	1:320	1:2560	1:1280
Auto antibodies	Anti-RNP	Anti-RNP	RF
	Anti-DNA	Anti-SSA	Anti-RNP
	Anti-SSA		Anti-Sm
	Anti-Sm		
LA	Positive	Positive	Negative
Maximum TR velocity	4.9 m/s (96 mm Hg)	5.5 m/s (121 mm Hg)	4.2 m/s (70 mm Hg)
Maximum mPAP at catheterization (mm Hg)	50	62	38
Maximum PVRI at catheterization (Units × m ²)	15.3	15.5	11
Peak oxygen consumption (% predicted VO ₂ max)	15.3 (mL/kg/min) (37)	14.2 (mL/kg/min) (26)	20.9 (mL/kg/min) (45)
Recent FVC (% of predicted FVC)	Not performed	1.87 L (69)	1.65 L (71)
Recent FEV ₁ (% of predicted FEV ₁)	Not performed	1.63 L (71)	1.64 L (81)
Recent DLCO (% of predicted DLCO)	Not performed	13.8 mL/min/mm Hg (54)	14.59 mL/min/mm Hg (82)
Recent 6MWD (m)	411	366	507
Recent BNP level (pg/mL)	74	45	29

ANA antinuclear antibody, BNP brain natriuretic peptide, DLCO carbon monoxide-diffusing capacity, DNA deoxyribonucleic acid antibody, LA lupus anticoagulant, RF rheumatoid factor, RNP ribonucleic protein antibody, Sm Smith antibody, SSA Ro antigen antibody, TR tricuspid regurgitation, 6MWD 6-minute walking distance

Table 2

Time course of disease

Case no.	Age (year-old)	PAH (TR velocity by echocardiography) m/s (mm Hg)	Systemic blood pressure (mm Hg)	PAH (PVRI by catheterization) (Units $\times$ m ²)	Symptoms related to CTD	ANA	Autoantibody	LA
1	14 (onset)	4.9 (96)	NA	4.6	None	1:320	Negative	Positive
	15	3.8 (58)	NA	1.4 (atrial septostomy)		1:320	Anti-SSA	
	16	4.2 (71)	NA	8.1 (atrial septostomy)		1:320	Anti-RNP	
	17	2.7 (29)	93/55	8.1 (atrial septostomy)	Joint pain	1:640		
	18	3.3 (44)	97/58	4.8		1:160		
	19	3.6 (52)	112/66			1:80	Anti-DNA, anti-Sm	
	20	4.4 (78)	103/65			1:320		
2	21	3.8 (58)	121/81					
	10 (onset)	4.5 (81)	NA	16.4	Raynaud sclerodactyly	1:2560	Negative	Positive
	11	4.9 (96)	NA	15.7 (atrial septostomy)	None	1:1280	Anti-RNP, anti-SSA	
	12	5.2 (108)	NA			1:640		
	13	4.9 (96)	110/65			1:1280		
	14	5.4 (117)	110/58	12.5 (atrial septostomy)		1:640		
	15	5.0 (100)	103/62			1:640		
3	16	5.2 (108)	109/60					
	17	5.2 (108)	108/58	17.7 (atrial septostomy)		1:160		
	18	5.5 (121)	109/60	14.2				
	19	4.8 (92)	111/68	16.2	ITP			
	8 (onset)	4.2 (71)	NA	11.0	Muscle and joint pain Sclerodactyly	1:320	Anti-RNP, RF	Negative
	9	2.8 (31)	NA	3.1		1:320		
	10				None	1:320		
	11	3.3 (43)	NA	4.6		1:640		
	12					1:160	Anti-Sm	
	13	2.4 (23)	129/78	2.7		1:80		
	14					1:320		
	15				TTP			
NA not available								