Lung Transplantation and Idiopathic Pulmonary Arterial Hypertension: A Case Study


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Over the past decade effective medical treatments for idiopathic pulmonary arterial hypertension (IPAH) have decreased but not eliminated the need for lung transplantation for this disease. Timing of referral for transplant and listing remain critical judgments in the management of many PAH patients but are still subjects of significant debate. National initiatives that have increased donor organs overall and changed their distribution have changed previous decision-making for many centers. A case is presented that illustrates issues in managing the patient in whom medical therapy has failed.

Case Description

The patient was a white woman, who presented to the pulmonary hypertension clinic for evaluation of dyspnea on exertion. The patient had been in her usual state of good health until approximately one month prior to presentation, when she began noticing dyspnea while walking up a flight of stairs. She also reported dizziness and tingling in her thighs with exertion. One week prior to presentation, she went to her local emergency room with similar complaints. Electrocardiography performed there revealed inverted T-waves in the inferior leads, but a nuclear stress test was negative for ischemia. Echocardiography at that time revealed normal left ventricular systolic function but a severely dilated right ventricle and an estimated right ventricular systolic pressure of 81 mmHg with slightly elevated brain natriuretic peptide (BNP). Further workup at that time revealed a negative pulmonary embolism protocol CT scan of the chest, negative overnight oximetry, negative HIV antibody, and negative antinuclear antibody (ANA).

Key Words—Lung transplantation, idiopathic PAH, echocardiography, lung allocation score, epoprostenol.

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Table 1. Serial Hemodynamic Measurements.

	Baseline	4 Months	10 Months	15 Months
Right atrial pressure (mmHg)	5	10	11	15
Pulmonary artery pressure (mmHg)	67/21/43	96/22/58	88/25/55	84/28/51
Pulmonary capillary wedge pressure (mmHg)	5	14	7	Unable to obtain
Cardiac output/ Cardiac index (L/min)/(L/min/m^2)	3.1/1.78	2.4/1.5	2.8/1.7	2.8/1.8
Pulmonary vascular resistance (dyn·s·cm^{-5})	1045	1473	1362	Unable to calculate

History

Past medical history included Raynaud's phenomenon, gastroesophageal reflux disease, **s**coliosis, **c**utaneous zoster, and **c**holecystectomy. The patient's only medication was loratadine, which she took for seasonal allergies.

The patient was a nonsmoker and denied any illicit drug use. She drank approximately four to five drinks per week. She was a school teacher. There was no family history of pulmonary hypertension. Raynaud's phenomenon existed in two siblings. Review of systems was negative except for the sensation of weakness and fatigue, and chronic back pain related to having mild scoliosis since childhood.

Physical Examination

On examination, she was resting comfortably in no acute

Table 2. Clinical Course.

Months	Pulmonary artery pressure (mmHg, echocardiographic)	6-minute walk distance (feet)	Exercise O2 saturation {%)	NYHA functional class	Treatment
Baseline	91	1436	81	III	None
4	96	1476	93	III	R
9	NT	1470	93	III	E + S
11	102	NT	NT	III	E + S + B
13	NT	1448	88	III-IV	E + S
15	91	1400	80	III-IV	LAS = 35, E + S
16	110	NT	NT	III-IV	LAS = 40, E + S
17	120	NT	NT	IV	LAS = 40, E + S
18	195	NT	NT	IV	LAS = 70, E + S

B = bosentan; E = epoprostenol; LAS = lung allocation score; NT = not tested; S = sildenafil.

distress. Her vital signs were notable for mild hypertension, with a blood pressure of 139/102 mmHg and a pulse of 86. Her room air saturation was 98%. Her lung exam was normal without crackles or wheezing. Her cardiac exam revealed prominent jugular venous pulsations without definite jugular venous distension, a loud pulmonic component of the second heart sound, and a soft murmur at the lower left sternal border that increased with inspiration, but no S3 or S4 gallops. There was right upper quadrant tenderness over her cholecystectomy scar, but no hepatomegaly or hepatojugular reflux. Her extremities were without clubbing, cyanosis, or edema. The remainder of her exam was unremarkable.

Testing

Repeat echocardiography at this institution revealed normal left ventricular size and function. The left ventricular cavity was D-shaped and the right ventricle was severely dilated, with reduced function. There was moderate tricuspid and pulmonic regurgitation. The other valves were considered normal. Right ventricular systolic pressure was estimated at 91 mmHg. There was a minimal pericardial effusion. There was no evidence of shunting on a bubble study. Right heart catheterization was performed to confirm the diagnosis, to fully assess pulmonary hemodynamic parameters, and to determine potential responsiveness to pulmonary vasodilators. Her initial hemodynamics revealed pulmonary hypertension with reduced cardiac output and a normal pulmonary capillary wedge pressure (**Table 1**). There was no response to vasodilator challenge with adenosine infusion. Initial functional status was graded as WHO functional class III.

Clinical Course

Based on the initial low cardiac output and her poor NYHA functional class, treatment with a continuous infusion of epoprostenol sodium was recommended. However, the patient declined and opted for oral therapy with sildenafil 20 mg orally three times daily along with anticoagulation, diuretics, and oxygen therapy with exertion. Over the next 5 months, sildenafil was increased to 40 mg, then to 60 mg three times daily, as the patient's condition clinically worsened (**Table 2**). Continuous intravenous infusion of epoprostenol sodium was eventually instituted approximately 6 months after initial presentation. The patient initially improved clinically, but required increased diuretics for fluid retention in the next 4 months. Epoprostenol was more aggressively increased, eventually reaching 74 ng/kg/min, and bosentan was added; however, the patient experienced significant edema with decompensated cor pulmonale necessitating its discontinuation.

The patient previously declined evaluation for lung transplantation but now consented to this. She was subsequently listed for bilateral lung transplantation approximately 15 months after initial presentation. The initial calculated lung allocation score (LAS) was 35. The patient continued with an accelerated clinical decline and an appeal for an LAS of 40 was made and granted. Low-dose dopamine infusion was eventually added for hypotension and was continued on an outpatient basis.

She was subsequently hospitalized for worsening hypotension, increasing pulmonary hypertension with pulmonary artery systolic pressures ~ 200 mmHg by transthoracic echocardiography, and the development of a moderate-to-large pericardial effusion. Because no donor lungs had been offered, an appeal for an LAS of 70 was made. To facilitate the appeal in light of the patient's dire clinical circumstances, direct contact was established between transplant center physicians and leaders of the United Network for Organ Sharing (UNOS), resulting in a reassigned LAS of 70.

No acceptable lung offers occurred. Septic shock and bacteremia complicated by anuric acute renal failure subsequently developed and the patient died without transplantation. An autopsy showed Heath grade VI changes of pulmonary hypertension.

Table 3. Assessing Risk of Poor Outcome in Pulmonary Arterial Hypertension.

Determinant	Higher Risk	Lower Risk
Evidence of right ventricular failure	Yes	No
Progression	Rapid	Gradual
WHO functional class	IV	II, III
6-minute walk distance	<325 m	>380 m
Brain natriuretic peptide	>180 pg/mL	<180 pg/mL
Echo findings	Pericardial effusion; significant right ventricular dysfunction	Minimal right ventricular dysfunction
Hemodynamics	High right atrial pressure, low cardiac index	Normal or near normal right atrial pressure and cardiac index

Adapted from McLaughlin VV, McGoon MD. Contemporary reviews in cardiovascular medicine. Pulmonary arterial hypertension. *Circulation.* 2006;114(13):1417-1431.

Discussion

This case illustrates at least three challenges of caring for PAH patients with advanced disease in whom medical therapy ultimately fails:

1. Initial treatment selection
2. Timing of referral and listing for lung transplantation
3. Issues of current lung allocation

Initial therapy selection for patients with PAH is often a subject of debate in many cases. Recent updated evidence-based guidelines as well as a review of the literature suggest consideration of infusion therapy with a prostacyclin in patients with advanced disease in functional class III or IV[1]and patients judged to be at high risk for worsening (**Table 3**).[2] This patient presented initially with a mixed picture of risk factors, showing depressed cardiac output with normal right atrial pressure and a small pericardial effusion, but a reassuring 6-minute walk distance of 1436 feet (437 meters). Although initial prostacyclin therapy was suggested, decision-making with patient input led to the initial selection of sildenafil. Subjective improvement of the patient as well as significant improvement in oxygenation occurred on this regimen without significant improvement in the already somewhat reassuring walk distance. Worsening of both clinical edema and right atrial pressure prompted reevaluation of treatment options and addition of epoprostenol. It is unclear but open to speculation whether the clinical course ultimately would have been different had infused prostacyclin been introduced earlier.

A second consideration is the timing of referral and listing. Lung transplantation has been reviewed in previous issues of *Advances in Pulmonary Hypertension*. Current consensus guidelines suggest consideration of transplant in patients with PAH in advanced functional class III or IV in whom medical management is failing or who do not improve.[3] These recommendations are broad and attempt to anticipate the need for transplantation. Actual listing recommendations include traditional factors associated with poor long-term outcomes in PAH patients. ISHLT 2006 consensus guidelines[1] for PAH patients include:

- Guidelines for referral
  - NYHA functional class III or IV, irrespective of ongoing therapy
  - Rapidly progressive disease
- Guidelines for transplantation
  - Persistent NYHA class III or IV on maximal medical therapy
  - Low (350 meter) or declining 6-minute walk distance
  - Failing therapy with intravenous epoprostenol, or equivalent
  - Cardiac index of less than 2 L/min/m^2
  - Right atrial pressure exceeding 15 mmHg

The current patient initially improved with therapy, delaying the need for transplantation as has been typically described[4] with subsequent rapid decline prompting reevaluation of previous decisions regarding transplantation. It is clear that while we now have an arsenal of effective medical treatments for IPAH, not all patients respond. Indeed, the autopsy findings showed the highest grade (Heath VI) changes of pulmonary hypertension despite 18 months of treatment. Second, the course can dramatically accelerate, as it did here in her final three months. Her excellent 6-minute walk distance was maintained over the initial 15 months and provided some reassurance of her clinical stability. However, her right atrial pressure was progressively increasing over the same period, indicating impending right heart failure. These observations raise the issue of whether listing for lung transplant should have occurred sooner.

A third discussion point of this case is the current adequacy of lung allocation systems for patients with PAH listed for lung transplantation. Once listed for transplantation, local organ availability and priority on the transplant list determine transplantation. Priority on the transplant list now is determined by a calculated LAS that was conceived to consider both the likelihood of survival with and without transplant using available physiologic parameters and diagnosis. Lung allocation scoring replaced previous time-based organ allocation systems in May 2005[5] for patients older than 12 years to offset previously observed inequities of waiting-list death rates. Diagnosis groups disadvantaged with the previous system included pulmonary fibrosis, cystic fibrosis, and pulmonary hypertension. Because patients with IPAH listed for lung transplantation continue to have high waiting-list mortality, an appeal mechanism was introduced

with the LAS, although guidelines for appeal remain broad. Little is known about the effect of this process. At least two articles reviewing the LAS have been published.[6,7] While the mechanism for appealing for a higher LAS is mentioned, what is not clear is how often appeals are made, how often they are granted, and how successful this process is.

Based on our experience with the appeal process, the following elements appear to be important:

- A short appeal time
- Some understanding or guidance regarding appropriate LAS requests
- Accurate communication with the review board

This case illustrates a number of the difficult issues related to the management of advancing PAH and the considerations of lung transplantation, and underlines the need for reexamination of current practices and clinical outcomes of patients with advanced disease who may be candidates for lung transplantation as a final option on failure of medical therapy.

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