Idiopathic Pulmonary Arterial Hypertension and Coexisting Nephrotic Syndrome with Minimal Change Disease

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Idiopathic pulmonary arterial hypertension (IPAH) is a rare but devastating disease that most often affects women in their 30s, and the diagnosis is usually based on exclusion. Minimal change disease (MCD) is the primary cause of nephrotic syndrome in children younger than 16 years of age. We report an unusual case of a 47-year-old male with MCD who was found to have IPAH. The patient's age, gender, initial clinical manifestations, and the unusual coexistence of both MCD and IPAH complicated the process of arriving at an accurate diagnosis.

Key Words: Bosentan • Idiopathic pulmonary arterial hypertension • Minimal change disease

INTRODUCTION

Idiopathic pulmonary arterial hypertension (IPAH) is a relatively rare but serious disease, with an estimated incidence of 5.9 cases per million in the general population. If left untreated, IPAH has a mean survival rate of 2.8 years from the time of diagnosis. Pulmonary hypertension is defined as a mean pulmonary artery pressure > 25 mm Hg at rest. IPAH is less common in men, with a female to male ratio of 1.7 to 1, typically diagnosed in men in their 40s, and women in their 30s.¹² Symptoms of IPAH include fatigue, palpitations, syncope, edema, and chest pain. Right-sided heart failure is a common manifestation in the late stage of the disease. We herein report the case of a 47-year-old male with nephrotic syndrome secondary to minimal change disease (MCD) who was diagnosed with IPAH, where the clinical manifestations of MCD made early diagnosis of IPAH a difficult task.

CASE REPORT

A 47-year-old male was admitted in August 2008, whose body weight had increased for one week, with decreased urine output, dyspnea on exertion, cough, and increasing edema for more than a month. His history was negative for major systemic diseases, use of illegal drugs or medications, except for analgesic use due to gouty arthritis. Chest radiograph revealed pulmonary edema (Figure 1). The patient had hyperlipidemia, hypoalbuminemia, massive proteinuria, abnormal serum creatinine level, and hypertension; all consistent with nephrotic syndrome. Renal biopsy demonstrated histological findings of focal mesangial proliferation and mild interstitial inflammation, compatible with MCD. He was treated with albumin transfusion, diuretics, oral prednisolone, valsartan, and atorvastatin, and was discharged after 10 days.

Follow-up in the nephrology clinic revealed that the proteinuria, hypertension, hyperlipidemia, hypoalbuminemia, and creatinine clearance levels were improved,
but other symptoms such as chest tightness, dyspnea on exertion, and edema of the lower extremities had not fully resolved. The administration of digoxin, diltiazem, and bronchodilators at a local clinic failed to improve the patient’s symptoms.

In January 2010, the patient was again hospitalized, this time suffering from a gradual onset of respiratory distress in association with angina. Physical examination revealed blood pressure of 120/82 mm Hg, respiratory rate was 24 breaths/min, and heart rate of 83 beats/min., with the jugular vein engorged to 6-7 cm above the sternal angle in the supine position with head elevated to 30 degrees. An accentuated P2 with a grade II-III/V1 pansystolic murmur was heard at the left lower sternal border on cardiac auscultation. Edema was noted in both legs. The arterial blood gas analysis (while the patient was receiving O2 by mask at 10 L/min) revealed a pH of 7.452; PaCO₂, 31.4 mm Hg; PaO₂, 82.2 mm Hg; HCO₃, 21.4 mmol/L; tCO₂, 22.4 mmol/L; base excess, -1.5 mmol/L; and oxygen saturation at 96.7%. Other laboratory data were within normal limits, except for a D-dimer level of 1.45 mg/L (reference value: < 0.55 mg/L). Electrocardiogram showed normal sinus rhythm, right axis deviation, inverted T wave in lead III AVF V1-6, Q wave in leads III AVF, and rR pattern on V1 (Figure 2). Pulmonary embolism was suspected. Cardiac ultrasonography showed mild aortic, mitral, and pulmonary valve insufficiency, and severe tricuspid valve insufficiency. The ejection fraction of the left ventricle was 71%, and the estimated systolic pulmonary artery pressure (PAP) was 48-53 mmHg (determined through tricuspid regurgitation jet measurement). The right ventricle and atrium were enlarged, and the interventricular septum shifted to the left ventricle during systole (Figure 2). No thrombus or mass lesion was identified. Chest computed tomography (CT) scan with and without contrast enhancement in axial and coronal planes from lung apex to diaphragm did not reveal any abnormality of the

![Figure 1](image1). Chest radiography and electrocardiography in August 2008. (A) Chest radiography: Borderline heart size. Ill-defined density at bilateral lower lobe with engorged pulmonary artery. Batwing appearance of bilateral lung field, indicating pulmonary edema. (B) Electrocardiography: Sinus rhythm. Right axis deviation. Inverted T wave in leads III, AVF, V1-4, prominent S wave in lead I and Q wave in lead III. Probably the right ventricular pressure overload caused these changes.

![Figure 2](image2). Echocardiography image and electrocardiography in January 2010. (A) Echocardiography: Parasternal short axis view. Enlargement of the right ventricle. The interventricular septum shifted to the left ventricle during systole, indicating high right ventricular pressure. (B) Electrocardiography: Normal sinus rhythm, right axis deviation, inverted T wave in lead III AVF V1-6, Q wave in leads III AVF, and rR pattern on V1.
pulmonary parenchyma, or in the great vessels.

The patient was treated with enoxaparin 60 mg, subcutaneously, q12h for 2 days, and then changed to warfarin with the dosage adjusted and maintained an international normalized ratio 2-3. Both drugs were discontinued after a lung ventilation-perfusion scan revealed a low probability of pulmonary embolism. He was also treated with nicorandil 5 mg tid for anginal symptoms, digoxin 0.125 mg qd for heart rate control and right heart failure, furosemide 40 mg qid to bid, and spironolactone 25 mg qd for control of edema. In an attempt to improve his respiratory status, the pneumonologist recommended aminophylline 100 mg tid with O₂ therapy adjusted from mask with O₂ at 6 L/min to nasal prong at 3 L/min, according to pulse oximeter readings, to maintain an O₂ saturation above 90%.

A series of examinations were performed to determine the cause of the patient’s pulmonary hypertension. Pulmonary function testing revealed a mildly restrictive pattern. Abdominal sonography was negative. The patient performed poorly in the 6-minute walk test, completing only 220 meters. During this test, with room air, oxygen desaturation was detected by pulse oximeter at 90% in pre-exercise, to 82% in post-exercise stage, with little response to a bronchodilator, persistent dyspnea, and tachycardia of 170 beats/min. Laboratory studies were negative for thyroid disorders and connective tissue diseases. Consultation with a rheumatologist excluded sclerodermia and other autoimmune diseases. A right-side cardiac catheterization revealed a mean pulmonary pressure of 50 mmHg. Cardiac output was 2.24 L/min/m² by Fick method. The patient did not tolerate measurement of wedge pressure, as this caused a severe cough. Adenosin was infused intravenously at a dosage of 50 ug/kg/min for the vasodilator test, but chest tightness developed and dyspnea worsened soon after the infusion. The infusion of adenosin was promptly discontinued, and the response to the vasodilator could not be obtained.

The patient was discharged after 10 days with some symptomatic improvement, and was instructed to use oxygen at home as needed.

We requested bosentan from the National Health Insurance Bureau (NHIB) as IPAH was confirmed. Though the patient was receiving diltiazem 30 mg tid, dyspnea increased and he progressed from New York Heart Association (NYHA) functional class II to III, when he was hospitalized again 3 weeks later, in March 2010. We discontinued diltiazem because of hypotension; we then tried sidenafil, which also was discontinued after 2 days due to hypotension. Bosentan 62.5 mg bid was initiated after approval of the NHIB. After 4 weeks of treatment with this dosage, his respiratory status continued to deteriorate to NYHA functional class IV, and he required oxygen by a non-rebreather mask at 10-15 L/min. The patient then subsequently required non-invasive positive pressure ventilation. Despite the above-mentioned treatment, his O₂ saturation remained at 75-85%. The patient’s edema also increased despite increased use of diuretics, though a normal serum creatinine level and creatinine clearance indicated that his renal function was not deteriorating. The dosage of bosentan was increased to 125 mg bid, empiric use of inhaled bronchodilators (terbutaline 2.5 mg q8h to q6h as necessary) and oral methyprednisolone 8 mg bid (decreased to 8 mg qd after 4 days) was administered, by the suggestion of our pneumonologist. Transference to a medical center and eventual lung transplantation were suggested, but refused by the patient. The above treatments appeared to partially stabilize his condition. Echocardiography indicated estimated PAP of 50 mm Hg as determined by tricuspid regurgitation flow. No signs of hepatotoxicity or anemia were observed after a month of bosentan therapy.

After 5 weeks of the abovementioned therapy, the patient experienced sudden hemodynamic collapse followed by apnea. He was intubated and put on mechanical ventilation. Chest radiograph revealed new infiltrates in the left lung field, and laboratory testing revealed leukocytosis, and possible pneumonia with septic shock. Despite hemodynamic support and antibiotic therapy, the patient died 2 days later.

**DISCUSSION**

A high index of suspicion is crucial for a correct diagnosis due to the insidious nature of IPAH. Gradual onset of effort-related dyspnea is the earliest symptom, with ongoing right ventricular failure, and lower extremity edema secondary to venous congestion, which occurs frequently. Fatigue, palpitations, and chest pain are com-
mon symptoms, and syncope may occur because of fixed or falling cardiac output.1

Secondary causes of pulmonary hypertension include thromboembolic disease, collagen vascular diseases, valvular or congenital heart diseases, pulmonary diseases, thyroid disorders, or liver diseases. In addition, human immunodeficiency virus (HIV) infection, and drugs such as appetite suppressants have also been reported to cause pulmonary hypertension. To rule out these etiologies requires substantial testing, including chest radiograph, electrocardiogram, cardiac and abdominal sonography, ventilation-perfusion lung scan, chest CT scan, pulmonary function testing, right-side cardiac catheterization, HIV testing, testing for evaluation of collagen vascular diseases (such as anti-double strain DNA, antinuclear antibodies, anti-scl-70 antibody), and thyroid function and liver function tests.2,3

Goals of the treatment of IPAH include improvement of quality of life, increasing exercise capacity, and prolonging survival. Digoxin, diuretics, and supplemental oxygen are indicated for management of right heart failure, and oral anticoagulants are also recommended as they have been associated with extending survival. Calcium channel blockers, if responsive to a vasodilator test, prostacyclin and its analogues, and inhaled NO have been reported to be helpful in improving symptoms of IPAH,4-6 but the last two drugs are not available at our institution. Sildenafil, a phosphodiesterase type-5 inhibitor, promotes pulmonary vasodilation by increasing levels of cGMP, an equivalent action to that of inhaled NO. Clinical trials evaluating the effects of sildenafil in the treatment of IPAH have shown it to be effective in improving 6-minute walk test performance and hemodynamic function,7 but our patient did not tolerate the drug due to its hypotensive effects.

Bosentan is an orally administered endothelin receptor antagonist (ERA), and acts on ET-1 receptors. It inhibits the vasoconstrictor effect of endothelin, thus reducing pulmonary vascular resistance. A clinical study has shown that the earlier treatment with bosentan begins, the less clinical deterioration occurs, as evaluated by NYHA functional class.8 The recommended dosage is 62.5 mg bid for 4 weeks, followed by a maintenance dose of 125 mg bid. Possible adverse effects include hepatotoxicity, headache, nasopharyngitis, flushing, edema, hypotension, palpitations, fatigue, pruritus, and decreased hemoglobin. Monthly monitoring of liver function and hematocrit is recommended. Bosentan is contraindicated in pregnancy and in moderate to severe liver disease. Ho et al conducted a study using serial plasma brain natriuretic peptide (BNP) determinations in 6 patients receiving bosentan therapy. A decline of plasma BNP level was observed, and this effect persisted in the first 12 months and seemed related to a more favorable clinical outcome. The authors concluded that serial plasma BNP evaluation may be helpful in clinical evaluation and management in patient with IPAH treated with bosentan.9

The patient presented herein had a full clinical manifestation of nephrotic syndrome: edema, proteinuria (> 3 g/day), hypoalbuminemia, hyperlipidemia, elevated plasma creatinine level, and acute renal impairment. Hypertension may occur in 43% of patients presenting with nephrotic syndrome. Approximately 80% of all cases of nephrotic syndrome in children involve MCD; on the other hand, adults only represent 10-20% of all patients with MCD. Most MCD cases in adults are idiopathic, though HIV infection, lymphoproliferative malignancies, and use of drugs such as analgesics, rifampin, and interferon account for a portion of the diagnosed cases. In our review of the literature, we found only one study on children which evaluated the relationship between pulmonary arterial hypertension and nephrotic syndrome,10 based on echocardiography TR velocity and estimated systolic PAP. Among 40 patients with nephrotic syndrome, compared to the control group evaluated in this study, only 7 (17.5%) had possible pulmonary hypertension, with an estimated systolic PAP > 40 mmHg. The authors could not find any relationship between speculated mechanisms such as hypercoagulable state induced thromboembolism, systemic hypertension and pulmonary edema to pulmonary arterial hypertension. Also, the sufficiency of that study’s evidence, and the strength of its conclusions are reduced due to the study’s limited number of patients, including a lack of data on adult patients.

In our case, the patient’s MCD was proven to be idiopathic, as no other cause was found even after substantial testing was completed. The patient’s age, gender, and manifestations of nephrotic syndrome did not make a diagnosis of IPAH likely during the first hospitalization. However, reviewing the patient’s history, IPAH
may already have then existed, as the chest radiograph and electrocardiography were abnormal (Figure 1), and contributing manifestations such as edema were present. A year later, during the second hospitalization, an abnormal D-dimer level and electrocardiogram findings suggested a diagnosis of pulmonary thromboembolism. IPAH was confirmed only after all testing excluding secondary etiologies had been performed. In spite of treatment for MCD and control of the nephrotic syndrome, standard management for heart failure, oxygen supplementation, and administration of bronchodilators, calcium channel blockers, sildenafil, and bosentan, the patient’s condition deteriorated, and he succumbed to a secondary infection.

In summary, IPAH is a devastating disease and a high level of suspicion is required to make an accurate diagnosis. Early initiation of treatment may improve the quality of life and exercise capacity, and extend patient survival.

REFERENCES