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A Diagnosis of Exclusion: Idiopathic Pulmonary Arterial Hypertension Presenting as Intractable Shortness of Breath - A Case Report & Review of the Subject

Talha Mahmud, Kamal Ashraf, and Muhammad Saqib
Department of Pulmonology, Shaikh Zayed Hospital, Lahore.

SUMMARY

A 35 year old house wife was evaluated for gradual onset and progressively worsening dyspnea. She had normal vitals, but raised JVP, loud P2, normal vesicular breathing in chest and normal systemic examination. Her chest radiograph showed cardiomegaly and echocardiography was consistent with severe pulmonary hypertension of non cardiac origin. Extensive investigations to find any cardiovascular, respiratory or systemic disorders were negative ruling out an underlying cause of occult pulmonary hypertension and she was finally diagnosed as having idiopathic pulmonary hypertension (IPAH). She responded well to treatment with pulmonary vasodilator drugs and was advised regular follow ups in pulmonary out patients department.

INTRODUCTION

Pulmonary hypertension is a life-threatening condition characterized by elevated pulmonary arterial pressure and secondary right ventricular failure. It is now classified by WHO in 5 groups according to underlying mechanisms. Patients experience exertional dyspnea, lethargy, and fatigue and exhibit loud second heart sound and signs of systemic venous hypertension. The two main diagnostic modalities include echocardiography which is used as a screening tool and right heart catheterization utilized as a confirmatory modality. The main management is according to the underlying cause with pulmonary arterial hypertension (group 1) requiring advanced therapy with specific agents that act on pulmonary vasculature. Therapy improves symptoms, exercise capacity, functional class as well as survival.

CASE REPORT

A 35 years old lady resident of Jhang was hospitalized through pulmonary out patients department after being referred from cardiology department for evaluation of intractable dyspnea due to pulmonary hypertension while receiving treatment with bosentan and sildenafil for 2 months. Six months ago, she developed dyspnea of gradual onset that worsened progressively with partial relief during rest periods. She now felt breathless (MMRC grade 4) even while performing routine household activities like going to toilet, working in kitchen etc. She was a never smoker and denied any addiction and had no significant past medical (other than the current problem) or surgical history (except asymptomatic cholelithiasis). She was married with three healthy children, had no pet animals or birds at home but admitted positive exposure smoke from burning of biomass fuel. She belonged to a middle social class and had no history of use of any anorexigens or other indigenous drugs. Her family & gynecological history was not contributory. On examination she was an average built young lady, well oriented and cooperative with following vitals: pulse: 74/min, regular, BP: 100/60 mmHg, respiratory rate 20 breaths per minute and temperature of 98°F and SpO_2 (on room air) 94%. She was pale with raised JVP 5 cm above sternal angle, normal heart sounds with loud P2, bilateral normal vesicular breathing in chest and normal abdominal, central nevous and musculoskeletal system examinations.

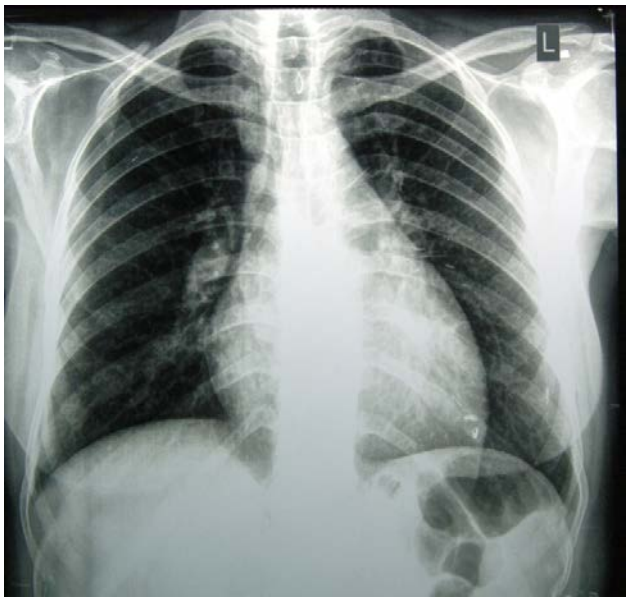

Fig. 1. Chest radiograph showing cadiomegaly, prominent central pulmonary vessels with bilateral clear lung fields.

Her chest radiograph showed cadiomegaly, prominent central pulmonary vessels with bilateral clear lung fields (Fig. 1) and ECG was consistent with right atrial and right ventricular strain and hypertrophy (Fig. 2). Complete blood count (CBC) showed HB 14.0 g/dl, WBC 8.79, platelets 26000/cmm, MCV 84.0 fl, MCH 28.5 pg, DLC (neutrophils 61.6% and lymphocytes 35.3%). Serum electrolytes, LFTs and RFTs were within normal limits. Further lab tests were carried out to rule out underlying causes of pulmonary hypertension including plasma BNP 915.6 pg/mL (suggestive of right ventricular failure) D-dimer levels were normal (ruling out venous thromboembolism as being provocative for persistent pulmonary hypertension), ANA & RA factor (autoimmune screening), viral serologies for hepatitis B, C & HIV (positive association with pulmonary hypertension) were also negative. Arterial blood gas analysis revealed pH 7.39, PO_2 82 mmHg, PCO_2 36 mmHg and HCO_3 24 mmol/L. SpO_2 on oximetry was 94% and declined to 82% (post exertional desaturation) while spirometry was consistent with mild restrictive dysfunction.

Prior to this hospitalization, she underwent echocardiography twice (both transthoracic and trans-esophageal) showing dominant right sided chambers (right atrial and ventricle) but no intra-cardiac shunt and severe pulmonary hypertension (PASP 85 mmHg), LV ejection fraction 63%, no abnormal segmental wall motion & normal valves except mild PR & TR. Her HRCT chest was clear for any airway, mediastinal or pulmonary parenchymal abnormality that could have cause hypoxemia and pulmonary hypertension (Fig. 3).

As there was no respiratory, cardiovascular, autoimmune or systemic cause, the final diagnosis was Idiopathic Pulmonary Arterial Hypertension (IPAH), being the diagnosis of exclusion. Her current treatment was escalated with bosentan 125 mg twice daily and sildenafil 25 mg thrice daily and beraprost 20 mcg thrice along with warfarin 5 mg and amiloride 25 mg daily. Her follow up was arranged after 2 months of treatment when she reported improvement in her exercise tolerance (MMRC dyspnea grade declined from 4 to 2). Beraprost was stopped and sildenafil and bosentan were continued and she was advised to regularly follow up on three months basis with LFTs (bosentan toxicity) and echocardiography.

DISCUSSION

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest & pulmonary capillary wedge pressure (PCWP) less than 15 mm Hg (based upon right heart catheterization measurements).[1] A mPAP of 8 to 20 mmHg at rest is considered normal, while a mPAP of 21 to 24 mmHg at rest has uncertain clinical implications. The newer WHO classification system has abandoned the term secondary pulmonary hypertension and the updated system now entails five classes of pulmonary hypertension including group 1 (pulmonary arterial hypertension/ PAH), group 2 (PH owing to left heart disease), group 3 (PH owing to lung diseases or hypoxemia), group 4 (chronic thromboembolic pulmonary hypertension) and group 5 being attributed to PH with unclear multifactorial mechanisms

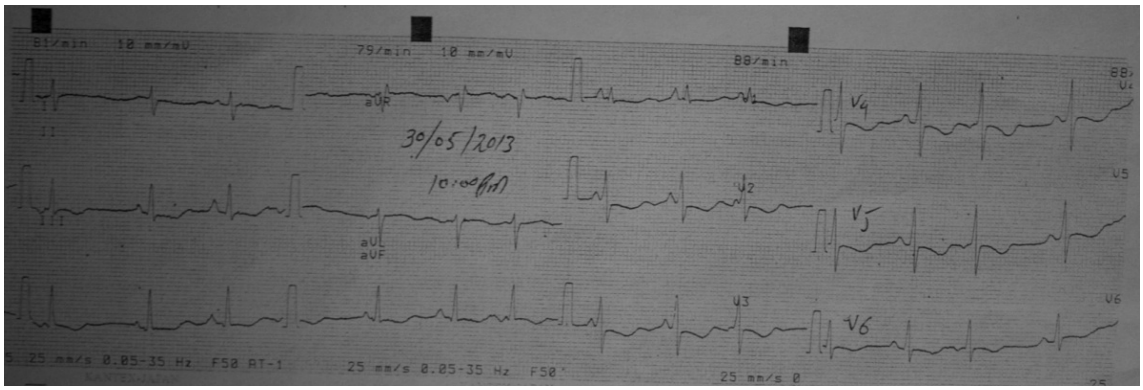

Fig. 2. ECG showing P pulmonale, R wave in lead V1 and inverted T waves in V1-V6.

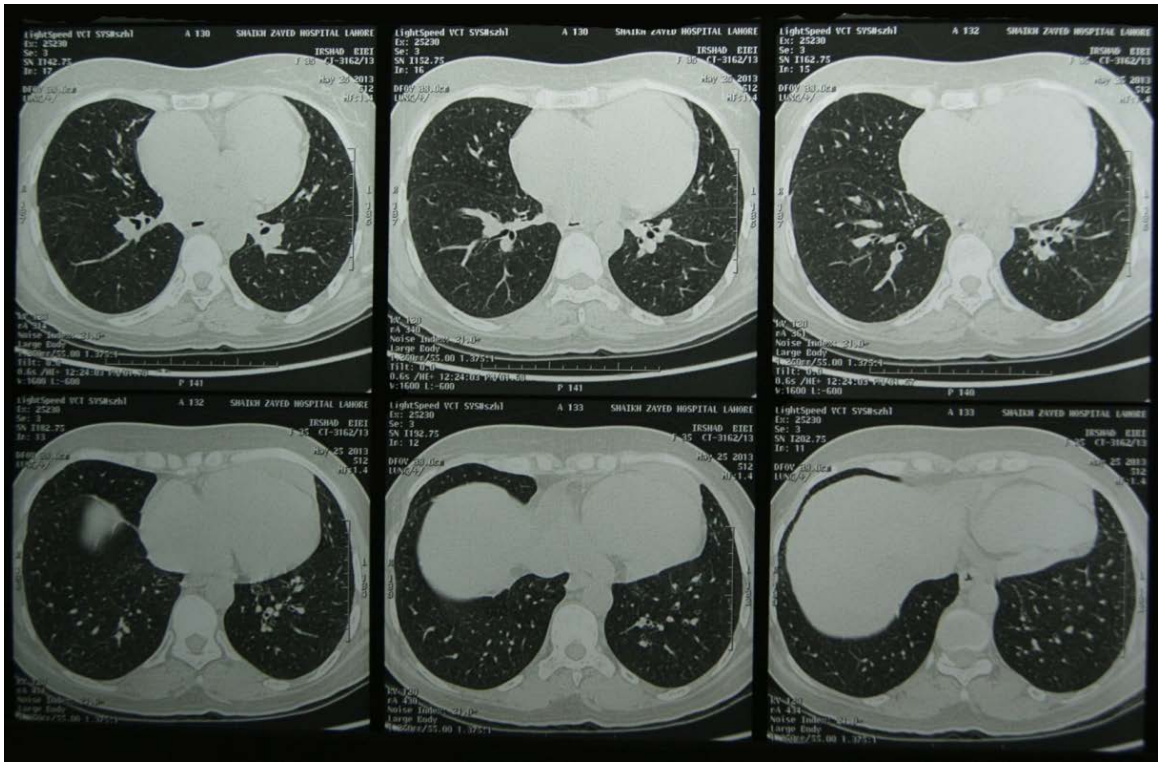

Fig. 3. HRCT chest showing cardiomegaly with normal airways and lung parenchyma.

e.g. sarcoidosis, chronic kidney disease and myeloproliferative disorders.[2] There is no data from Pakistan but one of the French studies showed the prevalence of group 1 PAH in the general population was estimated to be 15 cases per one million adults.[3] There are numerous causes of PAH including idiopathic pulmonary arterial hypertension (IPAH; both sporadic and hereditary), drugs (anorexigens) and toxins, connective tissue diseases, HIV infection, porto-pulmonary hypertension, and congenital heart disease.[2]

IPAH exists when an underlying cause of the PAH cannot be identified. It affects women more than men among persons between 20 to 40 years of age. Approximately 6% has a positive family history (FPAH), related to one of more than 70 identified

mutations in the gene-encoding bone morphogenetic protein receptor type II (BMPR2), at chromosome 2q33.[4] Pathogenetically, PH is a vasoproliferative disease (not vasoconstrictive) characterized by proliferation of all vascular layers (tunica intima, media and adventitia) invoked by mitogenic stimuli. The vascular changes also involve the pulmonary arteriole, and are characterized by vasoconstriction, vascular remodeling with intimal and medial proliferation, varying degrees of inflammation, the formation of plexiform lesions, and thrombosis. These changes lead to progressive obstruction of flow, increased pulmonary vascular resistance, and eventual right heart failure and death.[5] Most patients with PH initially experience exertional dyspnea, lethargy, and fatigue, which are due to an inability to increase cardiac output with exercise. As the disease progresses and right ventricular failure develops, exertional anginal chest pain, exertional syncope, and peripheral edema may develop.[6] With more advanced disease, the physical examination reveals signs of right ventricular dysfunction. The ECG most often reveals right atrial or right ventricular (RV) hypertrophy and right-axis deviation while the chest radiograph shows cardiomegaly consistent with RV hypertrophy, with enlarged pulmonary arteries.[7] For the diagnosis of IPAH, all those conditions (respiratory diseases and/or hypoxemia) which can cause pulmonary hypertension should be ruled out. A panel of respiratory evaluation tests should be carried out in specific conditions which may include spirometry, plethysmography, diffusing capacity, arterial blood gas measurement, CT scan of the chest and polysomnography in suspicion of obstructive sleep apnea.[1,2,7]

A patient is said to be suffering from IPAH if most of the conditions from all groups are ruled out and can be supported by genetic testing if available.[4] The best screening test for the detection of PAH is a transthoracic and in doubtful cases trans-esophageal echocardiogram (especially to rule out left-sided heart disease or intracardiac shunts which may require enhancement by intravenous injection of agitated saline).[7,8] Increased PASP on echocardiogram raises the possibility but is clearly not specific for PAH & further testing to identify the underlying cause is warranted. Echocardiography is imprecise in the measurement of pulmonary artery pressure (PAP) & cannot determine the pulmonary capillary wedge pressure (PCWP) & cardiac output.[8] Right heart catheterization is the gold standard test to establish severity and prognosis, measure PCWP, exclude congenital heart disease, and test the response to selective pulmonary vasodilators (*e.g,* inhaled nitric oxide (NO), or IV adenosine or epoprostenol). Measurements should include sequential oxygen saturation for the presence of an intracardiac shunt; pulmonary angiography for thromboembolic PH; and hemodynamic measurements including PAP, PA occlusion pressure, and cardiac index. A positive response to therapy with vasodilators is defined as a fall in mean PAP of >10 mm Hg to reach a mean PAP of <40 mm Hg, with an increased or unchanged cardiac output.[7]

The management of pulmonary hypertension includes treatment of the underlying cause in patients with group 2, 3 and 5, while for group 4 patients anticoagulation is the primary medical therapy & thromboendarterectomy remains the primary surgical treatment.[6,7] Group 1 PAH individuals and patients with non surgical candidacy in group 4 PH or those who fail surgical management should be offered advanced therapy. The drugs which are used in advanced therapy include prostanoids (prostacyclin analogues): beraprost, treprostinil (inhaled, IV or SC), iloprost (inhaled), epoprostenol (IV), endothelin receptor antagonists: bosentan and ambrisantan, phosphodiesterase 5 inhibitors: sildenafil, tadalafil and verdenafil and certain calcium channel blockers (used rarely).[1,9] World health organization functional class I patients (no limitations of physical activity) receive general care, oral therapies are the first-line agents for patients in functional class II (slight limitation of physical activity) and class III (moderate limitation of physical activity), whereas parenteral therapies are reserved for patients in class IV (inability to carry on any physical activity without symptoms).[1,10] It is not clear whether the sequential addition of agents is preferable to upfront combination approaches. It is also not clear which of several possible combinations of agents is most efficacious and at this time it is recommended that patients with class III to IV PAH who fail to

improve after 3 months on targeted therapy should be considered for combination therapy.[1,8,10] If pharmacologic treatment fails, surgical (the last resort) treatment including atrial septostomy or lung transplantation should be considered.[11]

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The Authors:

Talha Mahmud
Associate Professor & Head,
Department of Pulmonology,
Shaikh Zayed Hospital, Federal Postgraduate Medical Institute, Lahore, Pakistan.
drmtalha@hotmail.com

Kamal Ashraf
Trainee Registrar of Pulmonology,
Shaikh Zayed Hospital, Federal Postgraduate Medical Institute, Lahore, Pakistan.
kamal4923@ hotmail.com

Muhammad Saqib
Senior Registrar of Pulmonology,
Shaikh Zayed Hospital, Federal Postgraduate Medical Institute, Lahore, Pakistan.
malchik2000@hotmail.com

Address for Correspondence:

Talha Mahmud
Associate Professor & Head,
Department of Pulmonology,
Shaikh Zayed Federal Postgraduate Medical Institute, Lahore, Pakistan.
drmtalha@hotmail.com