HIV-Associated Primary Pulmonary Hypertension: A First Case Report in Thailand and Literature Review

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A 32-year-old woman had asymptomatic HIV infection diagnosed with primary pulmonary hypertension simultaneously. She presented after a three-month rapid progression of symptoms and hemodynamic change. Physical examination and laboratory findings were compatible with pulmonary hypertension. No sensible cause could be found for the pulmonary hypertension except the HIV seropositivity; therefore, HIV-associated primary pulmonary hypertension was diagnosed. She was treated with diltiazem and oral anti-coagulation. After four months, her functional status improved from a NYHA functional class of II to I and improved in right venticular function. Since HIV is epidemic, the authors recommend HIV testing in cases of primary pulmonary hypertension.

Keywords: *HIV, Primary pulmonary hypertension*

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Primary pulmonary hypertension (PPH) is an uncommon clinical syndrome characterized by sustained elevations of pulmonary artery pressure and pulmonary vascular resistance without any demonstrable cause[1-3]. In the registry of the National Institute of Health (NIH), diagnosis is confirmed by the presence of a mean pulmonary arterial pressure of > 25 mm Hg at rest or 30 mm Hg during exercise, and that secondary causes have been excluded[4].

The association between PPH and HIV infection is well established[5-9]. HIV-associated primary pulmonary hypertension (HPPH) has the same clinical features and pathological findings as classic-PPH[5-7,10-17]; but progression is more severe[6,8]. HPPH is a grave disease and has a poorer prognosis than classic-PPH. Half the patients die during the median follow-up of 8 months[7] compared with a median survival of 2.9 years in non treated classic-PPH[18]. The treatment of HPPH is not well defined; however, some reports reveal treatment with prostacyclin or antiretroviral therapy improves clinical status and patient survival[19-23].

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The authors report a case of primary pulmonary hypertension associated with HIV seropositivity at a tertiary referral hospital in Northeast Thailand.

Case Report

June 9th, 2003, a 32-year-old, non-smoking, Thai woman with no underlying disease was admitted to Srinagarind Hospital, Khon Kaen University, with a three-month history of progressive dyspnea on exertion (NYHA functional class II), fatigue, and leg edema. She had no history of orthopnea, paroxysmal nocturnal dyspnea, chest pain, cough, wheezing, fever, weight loss or Raynaud's phenomenon. She had taken oral contraceptives for two years but had stopped them three months before being admitted to hospital. She gave no history of ingestion of anorectic agents, amphetamines or cocaine. Moreover, no family history of pulmonary hypertension was given.

A month prior to admission, she went to a local hospital for transthoracic echocardiography: the right ventricle was dilated with moderate tricuspid regurgitation, the right ventricular systolic pressure (RVSP) was 55 mm Hg, the normal left ventricle (LVEF 76%), and no evidence of intracardiac shunting was found. She was diagnosed with pulmonary hyper-

tension and treated with diuretics, whereupon the edema of the leg resolved, but the dyspnea and fatigue did not. Thereafter, she was transferred to Srinagarind Hospital - a tertiary referral university hospital in Northeast Thailand.

On physical examination, she was afebrile and had a respiratory rate of 20/min. Cardiovascular examination revealed jugular venous distention, right ventricular heaving and a loud pulmonic component of the second heart sound, but no murmur or fixed splitting of the second heart sound. The lungs were clear on auscultation. There was no cyanosis, clubbing, hepatomegaly, peripheral edema, oral thrush, oral hairy leukoplakia or pruritic papular eruption. The results of the remainder of the examination were unremarkable.

Pertinent laboratory findings included: hemoglobin 14.7 g/dL; hematocrit 44.5%; platelet count 137,000/mm^3; leukocyte count 4,100/mm^3 with 33% segmented cells and 36% lymphocytes. Arterial blood gas analysis on room air revealed a pH of 7.378, a Po_2 of 88.4 mm Hg, and a Pco_2 of 29.5 mm Hg. The ECG showed sinus tachycardia (heart rate 104/min), right axis deviation, right atrial enlargement, right ventricular hypertrophy and occasional PVC. The chest roentgenogram showed mild cardiomegaly with prominent pulmonary arteries and pulmonary trunk, but without infiltrates. Tests for anti-nuclear antibodies, anti-dsDNA antibodies, LE cells, VDRLs, HBsAgs, anti-HBs antibodies, anti-HBc antibodies and anti-HCV, were all negative. A ventilation and perfusion lung scans revealed no evidence of pulmonary emboli.

The pulmonary function tests revealed: A forced vital capacity (FVC) of 2.44 L (90.04% of predicted); a forced expiratory volume in 1 sec (FEV_1) of 2.11 L (88.28% of predicted); and, a FEV_1/FVC of 86%.

An echocardiogram (two-dimensional and Doppler-color examination) demonstrated: a normal appearing left ventricle (LVEF 50%), a dilated pulmonary artery, an enlarged right atrium and a right ventricle with impaired systolic function, D-shaped paradoxical movements of the interventricular septum into the left ventricle during systole, moderate tricuspid regurgitation, mild pulmonic regurgitation and a right ventricular systolic pressure (RVSP) 82 mm Hg. Mitral valve prolapse was observed but without mitral regurgitation, minimal pericardial effusion, and no evidence of intracardiac shunting.

Serologic HIV screening tests were positive and her CD4 cell counts was 631.49 cell/mm^3. The presented patient denied using injected drugs or ever having had a blood transfusion; however, she had been tattooed three years prior. HIV testing of her husband was negative. The couple used a condom during sexual intercourse. The authors adduce the HIV infection was acquired during the tattooing.

The patient was prescribed oral anticoagulation therapy in addition to diltiazem. Four months on, follow up transthoracic echocardiogram demonstrated: a dilated pulmonary artery with RVSP 64.2 mm Hg, an enlarge right atrium and right ventricle, but no impaired systolic function of right ventricle, and a normal left ventricle(LVEF 53%). Her exercise-tolerance improved from a NYHA functional class of II to I.

Discussion

HIV infection is an independent risk factor for the development of PPH[7,11,24]: the association was first described in 1987[25]. Since then 233 cases of HPPH have been described[7-9,22,23,26-31]. The presented case is the first reported case of HPPH in Thailand, and she presented with clinical features and laboratory findings in accordance with pulmonary hypertension. There was no discernible cause for the pulmonary hypertension except the HIV seropositivity; therefore, HPPH was diagnosed. Even though our patient didn't perform pulmonary angiography in order to rule out chronic pulmonary thromboembolism, but normal ventilation and perfusion lung scans is sufficient to excluding pulmonary embolism in patient with PPH[9,32,33].

HPPH is rare; however, the incidence appears to be several thousand times greater among HIV-infected individuals than in the general population: annual incidence of PPH in general population is 1-2 cases per million[3] vs 0.5-0.57 percent for HPPH[11,19]. During the era of HAART, the survival of HIV-infected patients has improved; therefore, HPPH will likely be recognized with increasing frequency. Nevertheless, between 6 and 25 percent of HIV positivity was discovered at the time the pulmonary hypertension was diagnosed[5,7,23], as in the presented.

The development of HPPH occurs independently of: The HIV risk factors, the CD4 cell counts or the stage of HIV infection[6-7,11,19]. In 131 cases of HPPH reviewed, the CD4 cell counts ranged between 0 and 937 cell/mm^3 (mean 269 cell/mm^3)[7]. In the presented patient, the HPPH was coincident with an asymptomatic HIV infection (CD4 cell counts was 631.49 cell/mm^3).

HPPH has the same clinical features and lung pathology as classic-PPH[5-7,10,12,15,34]. But there

are some differences. First; at initial diagnosis HPPH is younger, less disabling, has favourable hemodynamics[5] and a shorter interval between symptom onset and diagnosis (6-9 months and 2.03 years, respectively)[4,6-8,23]. These differences are perhaps the result of the closer medical attention given to HIV-infected patients[5]. Notwithstanding, between 6 and 25 percent of HPPH plus HIV were first diagnosed with the development of pulmonary hypertension. It can be suggested that HPPH has more rapid progression than classic-PPH. As in the presented patient that rapidly progressed dyspnea within three months. Second; prognosis of HPPH is poorer than classic-PPH: median survival time is between 6 months and 2 to 3 years, respectively[2,7,18]. Most HPPH sufferers die from the sequelae of pulmonary hypertension (viz. right-sided heart failure, cardiogenic shock, and sudden death) rather than other complications of HIV infection[5,7,17,19,23]. All of these should suggest that, HPPH is a worse prognosis and more rapidly progressive disease than classic-PPH. In addition, PPH was a significant independent predictor of death in HIV-infected patients, with a median survival of 1.3 years in HPPH vs 2.6 years in HIV-infected patients without pulmonary hypertension[19].

HIV infection, therefore, represents a precipitating event in the development of PPH. Endothelial injury and dysfunction are important in the pathogenesis of PPH, which results in alteration of the balance between vasoactive mediators. The latter leads to migration of smooth muscle cells into the vascular wall and promotes a procoagulant state[2,14]. In HPPH, an indirect mechanism was hypothesized whereby the virus stimulates the host to release pro-inflammatory cytokines or growth factors (viz. endothelin-l, interleukin-lb, interleukin-6, tumor necrosis factor-a, platelet-derived growth factor) rather than a direct infection of the pulmonary artery and development of pulmonary arteriopathy[24,35-37].

Even though HIV is an important risk factor for the development HPPH, its incidence is only 0.5-0.57 percent. A significantly increased frequency of HLA-DR6 and HLA-DR52 occurred in HPPH[38] suggesting that HPPH reflects a genetically determined host response to HIV infection.

Currently, no consensus recommendation for the treatment of HPPH exists. There are scanty data on calcium-channel blockers (CCB) and anticoagulant therapy in HPPH. CCB is ineffective and produces significant side effects[19,37]. In fact, one study demonstrated treatment with warfarin or CCB was not associated with increased survival[23]. In the presented patient, an improvement in exercise tolerance was achieved with diltiazem and oral-anticoagulation therapy. Only long-term therapy with continuous intravenous epoprostenol improves hemodynamics, exercise tolerance and survival in severe-HPPH (NYHA functional classes III or IV)[21,23]. Other less invasive routes of prostacyclin therapy (viz. subcutaneous prostacyclin (treprostinil) and inhaled epoprostenol) reportedly improve exercise tolerance and hemodynamics[20,39].

The role of antiretroviral therapy in HPPH remains controversial: three published reports indicate a favourable effect on hemodynamics, symptoms and/or survival[19,22,23]. In contrast, Pellicelli et al[40] demonstrated worsening pulmonary hypertension despite highly efficacious antiretroviral therapy (including a protease inhibitor and a low serum HIV RNA viral load).

In summary, the present report represents the first case of HPPH in Thailand, which suggests HIV-testing should be recommended in the evaluation of PPH.

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ภาวะความดันเลือดในปอดสูงชนิดปฐมภูมิในผู้ป่วยติดเชื้อไวรัสเอ็ชไอวี: รายงานผู้ป่วยรายแรกในประเทศไทยและทบทวนวารสาร

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รายงานผู้ป่วยหญิงไทย อายุ 32 ปี ได้รับการวินิจฉัยเป็น HIV-associated primary pulmonary hypertension โดยผู้ป่วยมีอาการเหนื่อยง่ายมากขึ้นเรื่อย ๆ เป็นเวลา 3 เดือน ผลการตรวจร่างกายและการตรวจคลื่นสะท้อนหัวใจ (echocardiogram) เข้าได้กับภาวะความดันเลือดในปอดสูง (pulmonary hypertension) ผลการตรวจทางห้องปฏิบัติการอื่น ๆ ไม่พบสาเหตุของความดันเลือดในปอดสูง ยกเว้นผลการตรวจคัดกรองการติดเชื้อไวรัสเอ็ชไอวีได้ผลบวก ซึ่งผู้ป่วยไม่มีอาการและอาการแสดงของการติดเชื้อไวรัสเอ็ชไอวี โดยมีค่า CD4 631.49 เซลล์/มม^3 ผู้ป่วยได้รับการรักษาด้วยยาละลายลิ่มเลือดร่วมกับ diltiazem หลังการรักษา 4 เดือน อาการเหนื่อยหายเป็นปกติ ร่วมกับผลการตรวจคลื่นสะท้อนหัวใจซ้ำ พบว่าความดันในเส้นเลือดแดงพัลโมนารีลดลงและหัวใจห้องล่างขวาทำงานดีขึ้น คณะผู้รายงานแนะนำให้ตรวจ คัดกรองการติดเชื้อไวรัสเอ็ชไอวีในผู้ป่วยภาวะความดันเลือดในปอดสูงชนิดปฐมภูมิทุกราย