Complete Reversal of Severe Pulmonary Artery Hypertension After Antiretroviral Treatment in a 43-year-old Newly Diagnosed HIV-infected Male: A Case Report

Christmae Maxine P. Solon, MD,[1] Jeremyjones F. Robles, MD, [1,2] Gwendolyn Pepito, MD,[1,3] and Chatie Olasiman, MD[1,4]

Abstract

Background: Human Immunodeficiency Virus (HIV) infection can be complicated by pulmonary arterial hypertension (PAH-HIV) wherein it can occur in approximately 0.5% of HIV patients. The benefit of ART in treating PAH-HIV is unclear in this population. Data on its safety, efficacy, and effect on the progression of PAH are conflicting and limited. In this case report, improvement in PAH was noted after ART was started.

Case: A 43-year-old, male, patient with no comorbidities, consulted due to a five-month history of progressive dyspnea, body malaise as well as weight loss. The patient is heterosexual with multiple sexual partners, an injection drug user, and was previously worked up for HIV, Hepatitis B, and C with unremarkable results. Initially managed as a case of Pneumonia but on CT scan was found to have a suprahilar mass which showed chronic granulomatous features. The positive GeneXpert confirms Pulmonary Tuberculosis (PTB). However, dyspnea was noted to progress thus 2D echocardiography was done which revealed severe pulmonary arterial hypertension with normal left ventricular function. Rescreening for HIV turned out positive thus started on anti-retroviral therapy (ART) with a noted improvement of symptoms as well as improvement and eventual normalization in pulmonary artery pressure. One year after initial diagnosis, undetectable viral load for HIV and Hepatitis C were noted along with improvement in CD4 count.

Conclusion: This is a rare case of severe pulmonary hypertension as an initial presentation for HIV infection. The approach to patients with incidental PAH may include work-up for HIV especially when risk factors are present. ART treatment may provide a favorable therapeutic option if initiated early.

Keywords: Pulmonary Arterial Hypertension, Human Immunodeficiency Virus, Antiretroviral Therapy, Pulmonary Tuberculosis, Case Report

Introduction

Human Immunodeficiency Virus (HIV) infection can be complicated by Pulmonary Arterial Hypertension (PAH). The World Health Organization classifies patients with PAH into five groups based on etiology, and patients with HIV infection belong to group I, those who have Pulmonary Arterial Hypertension (PAH).[1] Patients with PAH associated with HIV (PAH-HIV) occur in approximately 1 in every 200 or 0.5% of HIV-infected patients.[2] However, its diagnosis is often overlooked due to its similarity with Idiopathic Pulmonary Hypertension. More importantly, its diagnosis does not correlate with the stage of HIV infection and its development.[1] Therefore, diagnosis of PAH-HIV requires confirmation of PAH by right heart catheterization and the exclusion of other causes, and confirmation of HIV infection by serologic testing.

This case report highlights the importance of further diagnostic work-up for patients presenting with incidental findings of PAH, which should include screening for HIV. This is a rare complication of HIV infection occurring only in 0.5% of cases.[2,3] The benefit of ART in treating PAH-HIV is unclear in this population. Data on its safety, efficacy, and effect on the progression of PAH are conflicting and limited. However, in this case report, improvement in PAH was noted after ART was started.

[1] Department of Internal Medicine, Cebu Institute of Medicine – Cebu Velez General Hospital
[2] Section of Endocrinology, Diabetes, and Metabolism, Department of Internal Medicine, Chong Hua Hospital
[3] Section of Pulmonology, Department of Internal Medicine, Perpetual Succour Hospital
[4] Section of Infectious Diseases, Department of Internal Medicine, Chong Hua Hospital, Cebu City, Cebu, Philippines
Corresponding author: Christmae Maxine P. Solon E-mail: maxinesolon@cim.edu.ph

Case Presentation

This is a case of a 43-year-old, male, single, unemployed patient with no known comorbidities (hypertension, diabetes, or asthma) who sought a consult at the outpatient department for vertigo and loss of consciousness. Heredofamilial disease includes hypertension on the maternal side. He is currently not on any maintenance medications. Physical examination was unremarkable. An electrocardiogram revealed sinus rhythm with nonspecific ST and T wave changes. Echocardiography later revealed concentric left ventricular remodeling with adequate contractility and normal left ventricular systolic function with grade I left ventricular diastolic dysfunction and normal right ventricular systolic function but with findings suggestive of right ventricular pressure overload and mild pulmonary hypertension. Chest X-ray was normal at this time. Referral to a cardiologist was made, and a 24-hour Holter monitoring was done, which revealed inferior wall ischemia with frequent premature atrial contractions (PACs) and premature ventricular contractions (PVCs). Metoprolol 50 mg twice a day and aspirin 80 mg once a day was started, which the patient had poor compliance with.

Five months after the initial visit, the patient sought a consult at a tertiary hospital due to progressive exertional dyspnea, body malaise, weight loss, and chronic cough. Upon admission, the patient was not in respiratory distress with the following vital signs: BP = 110/70 mmHg, HR = 98 bpm, RR: 28 cpm, and T=38.2°C. Neck veins were not distended, and chest and lung findings were unremarkable. Cardiovascular findings showed regular rhythm with distinct heart sounds with no murmurs. No noted edema on the extremities.

However, the chest X-ray revealed pneumonia in the right upper lung field; thus, Ceftriaxone 2g IV infusion q 24 hours and Clindamycin 600mg IV infusion every 6 hours were started and managed as a case of Community-Acquired Pneumonia, moderate risk. The patient was slowly improving with the medications. However, with the progression of infiltrates on repeat Chest X-ray, a chest CT scan was done, which revealed a spiculated right minimally enhancing suprahilar mass measuring 4.9 x 4.3 x 4.3 cm, likely a malignant neoplasm along with pneumonitis in the right upper and lower lobes as well as mediastinal lymphadenopathies likely metastatic. However, the fine-needle aspiration biopsy of the suprahilar mass showed chronic granulomatous disease. Sputum GeneXpert revealed a positive result indicating Pulmonary tuberculosis (PTB) and thus was started on Rifampicin 150 mg + Isoniazid 75 mg + Pyrazinamide 400 mg+ Ethambutol 275 mg (HRZE) 3 tablets orally once a day regimen.

Worsening of dyspnea (RR: 30-40 bpm) as well as the onset of orthopnea were subsequently noted; thus, repeat echocardiography was ordered, which revealed concentric left ventricular remodeling with adequate contractility and normal left ventricular systolic function with the dilated right ventricular and atrial dimension with normal right ventricular systolic function but with severe pulmonary hypertension and mild to moderate tricuspid regurgitation. Ideally, right heart catheterization should measure pulmonary artery pressure; however, this was not available in our institution. In addition, the patient was deemed unstable to be transferred to another hospital for the procedure.

The patient was started on Sildenafil 25 mg twice a day for seven days and discontinued. Other causes for PH were pursued. Autoimmune disease work-up for SLE was unremarkable. Due to the absence of chronic obstructive lung disease and interstitial lung disease with no history suggestive of a possible malignancy leading to a chronic thromboembolic disease, the patient was apprised for rescreening for HIV and Hepatitis B and C infection, which was initially negative three months before admission. Pertinent social history included multiple heterosexual partners and a history of needle sharing due to illicit drug use.

The repeat HIV and Hepatitis C (Genotype 1-subtype 1a) was positive with an initial CD4 count of 211 cells/ul. Antiretroviral treatment (ART) with Efavirenz 600 mg + Lamivudine 300 mg + Tenofovir disoproxil fumarate 300 mg once a day was started, and the patient was eventually discharged.

Two months later, repeat echocardiography still revealed concentric left ventricular remodeling but decreased pulmonary artery systolic pressure to 56 mmHg from 76 mmHg. The patient had good compliance with both ART and PTB treatment. As shown in *Table I* 2D echocardiography five months after hospital discharge revealed normalization of pulmonary artery pressure (36 mmHg from 56 mmHg) and a resultant normal right ventricular systolic function. Improvement of the CD4 count at 235 cells/ul was also noted.

Six months after discharge, the patient was declared cured of PTB. *Figure 1* shows the timeline of the patient's course from onset of symptoms until discharge and follow-up. Frequent outpatient monitoring showed a return to previous baseline functional capacity with good compliance to his ART with no adverse events reported. HIV RNA at this time was already less than 34 copies/ml with a CD4 count of 309 cells/µl. Upon following up a year after, HIV RNA and HCV RNA were already undetectable with a CD4 count of 653 cells/ µl.

Discussion

The diagnosis of PAH is usually nonspecific and often missed without a reasonable index of suspicion. Usual symptoms are often nonspecific, insidious, and overlap with other common conditions.[1] Work-up for autoimmune disease, left heart disease, lung diseases, and chronic thromboembolic disease are usually indicated once pulmonary hypertension has been identified. PTB and pneumonia cannot fully explain the severe PAH evident in the patient. In a review, PTB can cause severe PH if extensive destruction in the vascular bed due to parenchymal abnormalities. However, the generalizability of these findings has its drawbacks since

Table I. Comparison of Pulmonary Artery Pressure of the Patient.

Parameter	Prior to the diagnosis of HIV	Diagnosed with HIV	On Anti-retroviral Treatment	On Follow-Up Check-up
PAP by TR gradient	41 mmHg	76.5 mmHg	56 mmHg	33 mmHg
TAPSE	0.95 cm	1.8 cm	2.5 cm	2.3 cm
Ejection Fraction	65 %	73%	73%	67%
Interpretation	Mild pulmonary hypertension	Severe pulmonary hypertension	Mild pulmonary hypertension	Normal pulmonary artery pressure

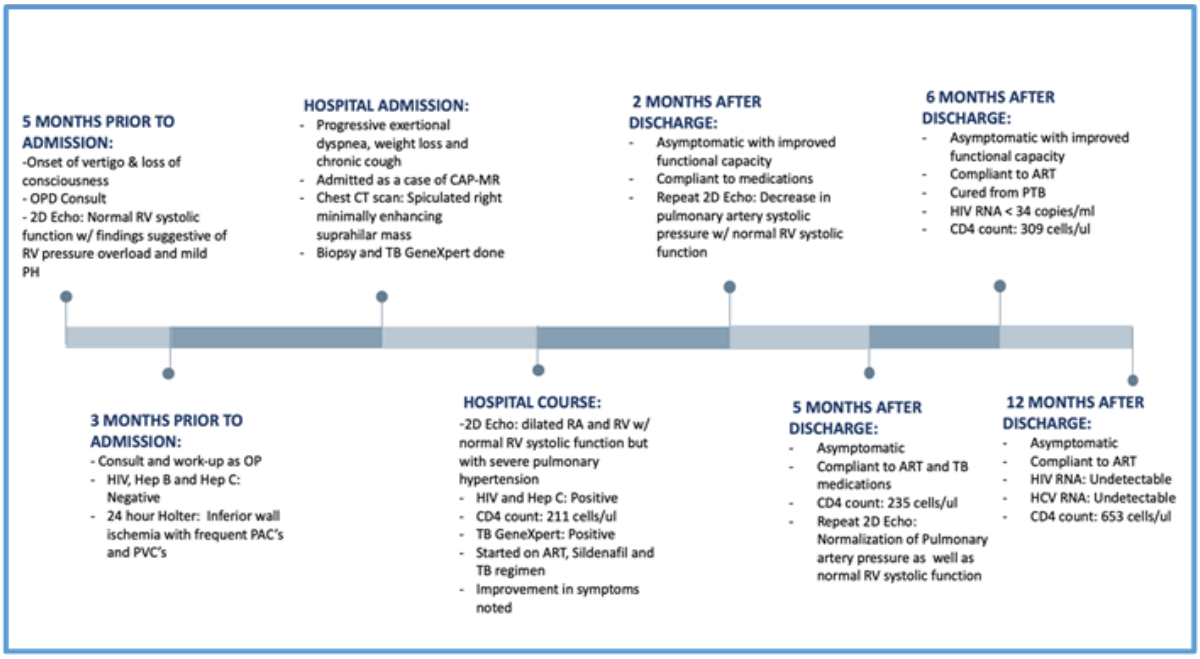

Figure 1. Timeline of the patient's course from the onset of symptoms until discharge and follow-up.

there are limited data on the population.[23] The patient, however, had normal chest X-ray findings with no signs of bronchiectasis three months before the diagnosis of PTB, which was also supported by the chest CT scan findings on admission. This makes the diagnosis of PH secondary to a chronic lung disease unlikely.

In most patients, the diagnosis of HIV infection is already present. Thus, PAH should be suspected in patients presenting with HIV who present with new symptoms suggestive of PAH. Rarely, HIV is discovered during routine evaluation of PH, as was evident in this case report. In a country such as the Philippines, which is experiencing the steepest rise in HIV incidence within the Asia Pacific Region with more than 170% increase in cases since 2010, incidental finding of PH warrants a possible work-up for HIV.[2]

PAH is a progressive, although rare complication of HIV occurring in 0.5% of cases.[3-11] A study conducted by Quezada et al. found out severe PAH-HIV developed in 0.8% of cases. The average duration from the detection of HIV infection until the onset of PAH-related symptoms is approximately two years or longer. However, PAH can develop during the early and late stages of HIV infection.[12] Predictors for PAH-HIV development are lacking; however, drug abuse and hepatitis C infection were noted to be risk factors for its development, increasing the risk threefold.[12] However, in this case, the patient presented initially with severe PAH. HIV and hepatitis screening was negative three months before its eventual diagnosis. The presence of concurrent hepatitis C and history of illicit drug use might have predisposed this patient to develop severe PAH.

The CD4 count does not predict the likelihood of developing PAH-HIV or its hemodynamic severity. Given the low rate of PAH-HIV, routine screening of asymptomatic patients with echocardiography is not typically performed. However, it is recommended for those who are symptomatic or with more than one risk factor (female sex, hepatitis C, origin from a high prevalence country).[17] Right heart catheterization is generally performed to confirm PAH, especially in patients in whom an etiology of PAH remains undetermined after extensive noninvasive investigations.

Although severe pulmonary hypertension was noted on 2D echocardiography for this patient, right heart catheterization was not done due to the unavailability of the procedure in our institution.

As of date, only limited data are available regarding PAH therapies for PAH-HIV. One study reported patients with PAH-HIV should be treated with measures targeting the specific factors contributing to PAH. In comparison, HIV is not known to infect endothelial cells, gp120, an HIV surface glycoprotein that stimulates the secretion of endothelin-1, a molecule known to contribute to idiopathic PAH (IPAH).[19] Another HIV protein, Tat, is an HIV transactivator that downregulates the expression of bone morphogenetic protein receptor type II (BMPR2). This molecule plays a role in IPAH and has been known to be downregulated in HIV-infected drug users and nef protein present in alveolar mononuclear cells and endothelial cells. In addition, HIV-nef gene polymorphisms are increased in patients with PAH-HIV compared to those with HIV without PAH.[20]

The benefit of ART in treating PAH-HIV is unclear and limited. In a study by Zuber et al., combination therapy with ART resulted in improved pulmonary measures with a median decrease of 25 mmHg in RA:RV gradient in doppler echocardiography and lower death rates.[14] Other studies found that although ART improved exercise capacity, it did not provide significant hemodynamic benefits.[22] For our patient, he was initially started on sildenafil; however, upon diagnosis of HIV, it was discontinued, and ART was started. The patient was compliant with ART treatment on subsequent outpatient follow-ups with the improvement of pulmonary artery pressures and functional status. CD4 count, HIV, and hepatitis C viral load also improved. This may likely be attributed to the effect of ART on the specific factors contributing to PAH. However, interpretation of the data is cautioned since pressures were not measured by right heart catheterization and treatment regimens were outdated and not the current clinical standard.[15]

Patients presenting with PAH-HIV may present more severe PAH often have a poor prognosis and usually die from its complications.[12] Compared with patients without HIV, PAH-HIV was an important predictor of death. In a meta-analysis conducted by Cicalini et al., survival rates were approximately 69% versus 38% in patients with PAH-HIV who began ART therapy compared to patients who did not.[16] One and three-year survival rates were approximately 88% and 72%, respectively, when ART was started.[17] In our patient, severe PAH-HIV was diagnosed relatively earlier than the median two years mentioned in the literature. ART was immediately started after that. This may have impacted the good prognosis and return to baseline functional capacity for this patient.

Conclusion

The incidental finding of pulmonary artery hypertension on 2D echocardiography may warrant further evaluation, including HIV work-up, especially when risk factors are present. Ideally, right heart catheterization should be done for these cases to confirm PAH. This unusual presentation of HIV was mitigated by a favorable response to ART with noted improvement on the patient's functional status and the complete reversal of the severe PAH on follow-up. However, data on the reversal of PAH is sparse after treatment with ART, and its initiation may provide a favorable therapeutic option if initiated early.

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