

Human Immunodeficiency Virus Associated Pulmonary Hypertension: A Case Report and Short Review

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Citation

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Abstract

We report a case of a young female who presented with dyspnea on exertion and was found to have pulmonary hypertension related to HIV infection. A brief review of current literature on pulmonary hypertension associated with HIV infection follows. HIV-associated pulmonary hypertension (PHT) is a well-recognized condition, with an estimated incidence of 1 in 200 HIV cases. Progressive shortness of breath is the most common presentation. Doppler echo study is a widely accepted as a tool to determine the pulmonary artery systolic pressure and lung biopsy is usually performed after workup for secondary pulmonary hypertension. There is no pathognomonic histopathological feature, though plexogenic pulmonary arteropathy is type most commonly seen. There seems to be no correlation between CD4 cell counts or history of opportunistic infection and the development or progression of pulmonary hypertension. HIV associated pulmonary hypertension is a diagnosis of exclusion. HIV patients present at a younger age, at an earlier stage with lower mean pulmonary artery pressure, and most importantly, run more aggressive course. Treatments with oral anticoagulation and calcium channel blockers have been disappointing. Some data showed that epoprostenol is promising. But its use is generally limited to seriously ill patients and a larger study with a long-term follow up is needed.

CASE REPORT

A 44 year old female with no significant past medical history, presented with progressive shortness of breath on exertion for 1 month. The shortness of breath was associated with dry cough and palpitation. The patient experienced decrease in functional class over a month. She used to walk eight blocks before, but now can only walk half a block limited by shortness of breath. She also had a three-pillow orthopnea, but did not recall any pressure-type chest pain on exertion, calf pain, rash or fever. Her internist for an asthma attack treated her without improvement in her symptoms. She denied any other medical problems in the past or to taking any elicit drugs but did report having smoked a few cigarettes a day for the past 20 years until a month ago. She had no significant family history.

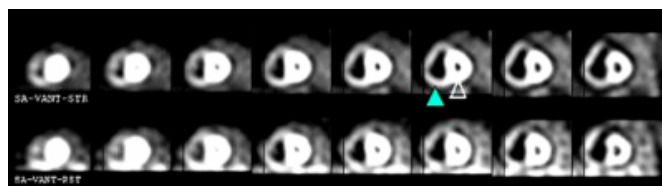
On physical examination, she was a well-built, well-nourished young female with normal blood pressure of 100/60, heart rate of 106 beats per minute and mild dyspnea at rest with a respiratory rate of 18/min. She was alert and oriented. No jugular venous distension or carotid bruit was noted. The cardiovascular examination revealed normal apex beat, normal heart sounds, and tachycardia with gallop heart sound. Lungs were clear to percussion and auscultation.

Abdominal examination was unremarkable. Extremities showed symmetrical pulse and no pedal edema.

The ECG showed sinus rhythm with T wave inversion in leads III and V1-V3. The T wave inversion in leads V1-V3 was new compared to a prior ECG done two months ago. The patient was referred to the cardiologist for a nuclear stress test to rule out myocardial ischemia. The patient underwent an exercise stress test with myocardial perfusion imaging using Tc-99m Sestamibi. The stress ECG and myocardial perfusion imaging were normal with a severely enlarged right ventricle (see Figure 1).

Figure 1

Figure 1: Myocardial perfusion images in short axis (stress and rest). Open arrowhead showing left ventricle cavity and shaded arrowhead showing severely dilated right ventricle cavity.



The patient was admitted to rule out pulmonary embolism.

Chest film showed mild cardiomegaly, enlarged pulmonary trunk and branch pulmonary arteries. Arterial blood gas on room air revealed chronic respiratory alkalosis with a high alveolar-arterial gradient. An echocardiogram was done to evaluate the chamber size and function, which revealed right ventricular dilatation with flattening of the septum, D-shaped ventricle and paradoxical septal motion, dilatation of the pulmonary trunk and bifurcation but no obvious thrombus was seen. These were new changes compared to normal echocardiogram ten months earlier. Spiral CT of the chest was done which showed no evidence of pulmonary embolism. A ventilation-perfusion scan was also done which was reported as low probability for pulmonary embolism. A right heart catheterization was done to evaluate the right-sided pressures and it revealed a right atrial pressure of 6 mmHg, right ventricular pressure of 58/6 mmHg, severe pulmonary hypertension with a pressure of 60/30 mmHg and a pulmonary capillary wedge pressure of 7 mmHg. Pulmonary consult was called and a lung biopsy was suggested to rule out pulmonary hypertension due to pulmonary parenchymal diseases. The lung biopsy showed lymphocytic infiltrate suggestive of lymphocytic interstitial pneumonitis. Microbial stains were negative. Patient was also tested for HIV infection, which came back positive with a CD4 cell count of 195. Patient was seen by infectious disease specialists and started on antiretroviral treatment. Subsequent to an effective antiretroviral treatment a significant improvement in pulmonary hypertension as well as right ventricle size was observed.

REVIEW OF LITERATURE

Because of the recent advances in antiretroviral therapy, patients who are infected with the Human Immune Deficiency Virus (HIV) tend to live longer.^{1, 2} Furthermore, non-infectious complications have become a more frequent cause of morbidity and mortality. Cardiac involvement from non-opportunistic infection in AIDS patients was first reported in 1983 in an autopsy case with myocardial Kaposi's Sarcoma.³ Approximately 28 to 73% of AIDS patients have been reported to have cardiac involvement,⁴ with the most common form being pericardial effusion, which has been reported to be as frequent as 20 % (range 10-40%).^{5,6,7,8} Pulmonary hypertension in AIDS patients or HIV-associated pulmonary hypertension (PHT), as in our demonstrated case, has been well recognized as a noninfectious complication in these patients.

INCIDENCE

Since first reported by Kim and Factor in 1987,⁹ HIV-

associated PHT has been increasingly described in the literature. Until October 2000, 131 cases have been reported in the world literature.¹⁰ The accurate incidence of HIV-associated PHT is unknown, but estimated to be 1 in 200 HIV cases, according to a study in 1989 by Hilmelman, et al.¹² Its incidence in the general population averages 1 in 200 000. This incidence should be as high as 7.1-8% among HIV or AIDS patients who presented with cardiopulmonary symptoms and signs.^{13, 14}

PATHOGENESIS

The pathogenesis of HIV associated PHT is not yet determined. The hypothesis of direct effect of HIV on pulmonary vascular endothelium or smooth muscle has not been proved in vivo. Mette, et al. failed to demonstrate HIV in pulmonary vascular endothelium in these patients, who have primary pulmonary hypertension, with electron microscopy, immunohistochemistry, DNA in situ hybridization and PCR techniques.²⁷ It has become more evident that HIV may indirectly stimulate the vascular endothelium and smooth muscle cell growth, along with vasoconstriction via some mediators and cytokines. In patients with PHT, the increase in serum interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-) concentrations,²⁸ supported this hypothesis. Furthermore, serum endothelin-1 also increased in these patients.²⁹ The link to HIV was clearer when the HIV glycoprotein gp 120 was found to stimulate endothelin-1 and TNF- secretion from macrophages in these patients in a concentration-dependent fashion.³⁰ The other possibility is autoimmune phenomenon, since HIV associated PHT patients have been reported to have significantly higher serum anticardiolipin IgM, anti SS-B and neopterin compared with matched control subjects.²⁵ At last, genetic predisposition may play a major role in susceptibility to developing PHT in HIV patients, evidenced by only a small proportion of HIV patients developing this problem. Morse, et al. found the significant increase frequency of HLA-DR6 and of HLA-DR52 in the HIV patients with PHT compared with non-HIV matched subjects and HIV matched subjects who do not have PHT.

CLINICAL FEATURES

The largest collective review to date¹⁰ showed that progressive shortness of breath is the most common presentation, along with pedal edema, non-productive cough, fatigue, syncope or near-syncope and chest pain. Physical findings include the common signs of pulmonary

hypertension, i.e. jugular venous distension, a loud P2, right-sided S3 gallop, tricuspid and pulmonary regurgitation murmur and peripheral edema. (Table I) There seems to be no correlation between CD4 cell counts (range from 0 to 937 cells/mm³, mean 269) or history of opportunistic infection and the development or progression of HIV associated pulmonary hypertension.¹⁰ But Pellicelli and colleagues did report a statistically significant difference between HIV positive patients with AIDS and those without AIDS with regard to degree of pulmonary hypertension, with AIDS patients having a higher pulmonary artery systolic pressure.¹¹

Figure 2

Table 1: Clinical Manifestations and Laboratory findings in HIV-associated PHT

Clinical Manifestations	Frequency (%)
Symptoms:	
Progressive shortness of breath	85
Leg swelling	30
Non-productive cough	19
Fatigue	13
Syncope/near-syncope	12
Chest pain	7
Signs:	
Jugular venous distension	NA
Loud P2	
Right sided S3 gallop	
TP or PR murmur	
Pedal edema	
Laboratory findings:	
<u>Chest X-ray:</u>	
Cardiomegaly	72
Prominent PA	71
<u>ECG:</u>	
RV Hypertrophy	67
Right Axis Deviation	21
Right Atrial enlargement	17
Sinus Tachycardia	16
<u>Echocardiography:</u>	
RV enlargement	98
Tricuspid Regurgitation	64
Paradoxical septal motion	40

DIAGNOSIS

As in idiopathic primary pulmonary hypertension, HIV associated pulmonary hypertension is a diagnosis of exclusion. Secondary causes of pulmonary hypertension, i.e. chronic hypoxemia, chronic pulmonary diseases, pulmonary thromboembolism, portal hypertension and talc granuloma (especially in IV drug abusers) must be sought and excluded. Provisional diagnosis is usually made by an echocardiogram. Doppler echo study is widely accepted as a tool to determine the pulmonary artery systolic pressure.¹⁵ Right heart catheterization usually confirms the diagnosis, and reveals elevated right-sided filling pressure and high pulmonary artery pressure with essentially normal pulmonary capillary wedge pressure. Mehta et al reported that the average

pulmonary artery pressure in HIV associated PHT was (mean \pm SD) $67 \pm 18 / 40 \pm 11$ mmHg, with systolic pulmonary pressure range from 33 to 120 mmHg and diastolic pressure ranging from 21 to 70 mmHg.¹⁰ Lung biopsy is usually performed after workup for secondary pulmonary hypertension, i.e. arterial blood gas, pulmonary function testing and ventilation-perfusion scan, reveals no positive cause. Pulmonary histopathology¹⁰ demonstrated plexogenic pulmonary arteriopathy in 78% of the patients, medial hypertrophy and intimal fibrosis without plexiform lesion 11%, pulmonary veno-occlusive disease 7%, and thrombotic pulmonary arteriopathy 4%. Although plexogenic pulmonary arteriopathy is the most common histopathological feature in HIV associated PHT, it is not pathognomonic. There are some other medical conditions i.e. portal hypertension, chronic hepatitis with liver cirrhosis, connective tissue diseases, and some type of congenital heart diseases, reported to have pulmonary arteriopathy type pulmonary hypertension.^{16,17,18,19}

TREATMENT

To date, there is no known certain therapeutic approach to the patients with HIV associated PHT. Most patients receive supportive treatment for right-sided heart failure and pulmonary hypertension, such as oxygen supplement and diuretics. Oral anticoagulation have shown to significantly improve survival in patients with non-HIV related primary PHT^{15,20} but results in HIV associated PHT has not been conclusive enough to encourage the use in this group of patients.^{12, 21,22,23} Treatment with oral calcium channel blockers, which have shown to improve survival in subgroups of non-HIV related primary PHT patients, have discouraging data in HIV associated PHT.^{24, 25} Only Epoprostenol, an intravenous prostacycline, has been reported to improve hemodynamic and functional status acutely^{24, 26} and in the long run (12-40 months).²⁶ Also, there is no difference in response to epoprostenol therapy between HIV associated PHT compared with primary pulmonary hypertension patients.²⁴ Epoprostenol therapy is generally limited to seriously ill patients²⁶ because of its cost and the need for continuous intravenous infusion. The role of antiretroviral agents in HIV associated PHT have been disappointing. Some data showed to decrease right heart pressure with antiretroviral medications²⁵ but some study showed no clinical benefit, but rapid deterioration of clinical course in some patients.¹⁴

CLINICAL COURSE

Compared with primary pulmonary hypertension, the patients with HIV associated PHT present at a younger age, at a lower mean pulmonary artery pressure and at the lesser degree of disability, classified by NYHA.²⁴ Nevertheless, PHT in HIV patients run a more aggressive course, shown by having the same survival rate at two year follow up (46% and 53%).²⁴ In the same study, most of the HIV patients (80%) died from pulmonary hypertension at one year.²⁴ A second study of HIV associated PHT reported a survival rate of 58% at one year with a median survival of 1.3 years, compared to 2.6 years in matched controls HIV patients without PHT ($P < 0.05$).²⁵ In other words, the presence of pulmonary hypertension in HIV patients reduces the probability of survival by 50%.

CONCLUSION

HIV associated PHT has been a well recognized condition. The association between these two conditions is more than a coincidence, since the incidence of pulmonary hypertension in HIV patients is 1000 times higher than in the general population. The presentation, hemodynamic profile, the lung histo-pathology and the response to epoprostenol, are not different from primary pulmonary hypertension, except that HIV patients present at a younger age, at an earlier stage with lower mean pulmonary artery pressure, and most importantly, run more aggressive course. Treatments with oral anticoagulation and calcium channel blockers have been disappointing. Although some data showed that epoprostenol is promising, a larger study population and a better-designed study with a long term follow up is needed before a standard recommendation can be made.

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References

1. Enger C, Grahm N, Peng Y, et al. Survival from early, intermediate, and late stage of HIV infection. *JAMA*. 1996; 275:1329-1334.
2. Mocroft A, Youle M, Morcinek J, et al. Survival after diagnosis of AIDS: a prospective observational study of 2625 patients. *BMJ*. 1997; 314:409-413.
3. Autran B, Gorin I, Leibowitch M, et al. AIDS in a Haitian woman with cardiac Kaposi's Sarcoma and Whipple's disease. *Lancet*. 1983; 1:767-768.
4. Kaul S, Fishbein MC, Siegel RJ. Cardiac manifestations of Acquired Immune Deficiency Syndrome. *Am Heart Journal*. 1991; 122:535-544.
5. Fink L, Reichel N, Sutton MG. Cardiac abnormalities in Acquired Immune Deficiency Syndrome. *Am J Cardiol*. 1984; 54:1161-1163.
6. Strang JI, Kakaza HH, Gibson DG, Girling DJ, et al. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *Lancet*. 1987; 2:1418-1422.
7. Reilly JM, Cunnion RE, Anderson DW. Frequency of myocarditis, Left Ventricular dysfunction and ventricular tachycardia in Acquired Immodeficiency Syndrome. *Am J Cardiol*. 1988; 62: 789-793.
8. Hecth SR, Berger M, Van Tosh, Croxon S. Unsuspected cardiac abnormalities in the Acquired Immune Deficiency Syndrome: an echocardiographic study. *Chest*. 1989; 96: 805-808.
9. Kim KK, Factor SM. Membranoproliferative glomerulonephritis and plexogenic pulmonary arteriopathy in homosexual man with acquired immune deficiency syndrome. *Hum Pathol*. 1987; 18: 1293-1296.
10. Mehta NJ, Khan IJ, Mehta RN, Sepkowitz DA. HIV-related pulmonary hypertension; analytical review of 131 cases. *Chest*. 2000; 118: 1133-1141.
11. Pellicelli AM, Barbaro G, Palmieri F, Girardi E, D'Ambrosio C, Rianda A, Barbarini G, Frigiotti D, Borgia MC, Petrosillo N. Primary pulmonary hypertension in HIV patients: a systematic review. *Angiology*. 2001 Jan; 52(1):31-41.
12. Himelman RB, Dohrmann M, Goodman P, Schiller NB, Starsken NF, et al. Severe pulmonary hypertension and cor pulmonale in the Acquired Immunodeficiency Syndrome. *Am J Cardiol*. 1989; 64: 1396-1399.
13. Speich R, Jenni R, Opravil M, Pfab M, Russi EW. Primary Pulmonary Hypertension in HIV infection. *Chest*. 1991; 100: 1268-1271.
14. Pellicelli AM, Palmieri F, Ambrosio CD, et al. Role of Human Immunodeficiency Virus in Primary Pulmonary Hypertension; case reports. *Angiology*. 1998; 49: 1005-1011.
15. Rubin LJ, Batst RJ, Kauser LR, et al. Primary Pulmonary Hypertension. *Chest*. 1993; 104: 236-250.
16. Edwards BS, Weir RJ, Edwards WD, Ludwig J, et al. Coexistent pulmonary and portal hypertension: morphologic and clinical features. *J Am Coll Cardiol*. 1987; 10: 1233-1238.
17. Rich S. Primary Pulmonary Hypertension. *Prog Cardiovasc Dis*. 1988; 31:205-238.
18. Hadengue A, Benhayoun MK, Lebrec D, Benhamou JP. Pulmonary Hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. *Gastroenterology* 1991; 100: 520-528.
19. Edwards WD. Pulmonary Hypertension and related vascular diseases. In: Stehbens WE, Lie JT, editors. *Vascular Pathology*. London: Chapman & Hall Medical; pp 585-621.
20. Fuster V, Steele PM, Edwards WD, Gersh BJ, et al. Primary Pulmonary Hypertension: natural history and the importance of thrombosis. *Circulation* 1984; 70: 580-587.
21. Jacques C, Richmond G, Tierney L, et al. Primary Pulmonary Hypertension and Human Immunodeficiency Virus infection in a non-hemophilic man. *Hum Pathol* 1992; 23: 191-194.
22. De Lassence A, Fleury-Feith J, Escudier E, et al. Alveolar hemorrhage. Diagnostic criteria and results in 194 immunocompromised hosts. *Am J Respir Crit Care Med* 1995; 151: 157-163.
23. Conraads VM, Colebunders RL, Boshoff C, et al. Primary Pulmonary Hypertension in a patient with HIV infection. *Acta Cardiol* 1998; 12:1404-1408.
24. Petitpretz P, Brenot F, Azarian R, et al. Pulmonary Hypertension in a patient with HIV infection: comparison with primary pulmonary hypertension. *Circulation* 1994; 89:

2722-2727.

25. Opravil M, Pechere M, Speich R, et al. HIV-associated Primary Pulmonary Hypertension: a case control study. *Am J Resp Crit Care Med* 1997; 155: 990-995.

26. Aguila RV, Farber HW. Epoprostenol (prostacyclin) therapy in HIV-associated Pulmonary Hypertension. *Am J Resp Crit Care Med* 2000; 162: 1846-1850.

27. Mette SA, Palevsky HI, Pietra GG, et al. Primary Pulmonary Hypertension in association with human immunodeficiency virus infection: a possible viral etiology for some forms of hypertensive pulmonary arteriopathy. *Am*

Rev Respir Dis 1992; 145: 1196-1200.

28. Humbert M, Monti G, Brenot F, et al. Increased interleukin-1 and interleukin-6 concentration in severe Primary Pulmonary Hypertension. *Am J Respir Crit Care Med* 1995; 151: 1629-1631.

29. Cacoub P, Dorent R, Nataf P, et al. Endothelin-1 in the lungs of patients with pulmonary hypertension. *Cardiovasc Res* 1997; 33: 196-200.

30. Ehrenreich H, Rieckmann P, Sinowatz F, et al. Potent stimulation of monocytic endothelin-1 production by HIV-1 glycoprotein 120. *J Immunol* 1993; 150: 4601-4609.

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