

Human Immunodeficiency Virus Associated Pulmonary Arterial Hypertension: An uncommon etiology of Pulmonary Hypertension

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Abstract: Pulmonary arterial hypertension has a deadly association with Human immunodeficiency virus infection. The incidence of pulmonary hypertension in Human immunodeficiency virus infection is higher than those in general population. This association significantly increases the mortality in these patients. We report a case of Human immunodeficiency virus infection who presented with cough, fever and severe shortness of breath. He was found to also have severe pulmonary arterial hypertension. He was managed with highly active anti-retroviral therapy and pulmonary vasodilators. The patient could not tolerate therapy and succumbed to his illnesses.

Keywords: Human immunodeficiency virus, Pulmonary arterial hypertension.

INTRODUCTION

Human immunodeficiency virus (HIV) related pulmonary arterial hypertension is an uncommon association. The pathogenesis of pulmonary hypertension in human immunodeficiency virus infection is not well understood but this association has poor prognosis. Pulmonary arterial hypertension occurs independently of other risk factors such as chronic hepatitis-C infection, portal hypertension, cirrhosis, intravenous drug use and autoimmune diseases [1]. The exact incidence of primary pulmonary hypertension in HIV positive patients is unknown, but appears higher than in the general population [2, 3]. Correlation between CD4 count or stage of HIV infection and prevalence or severity of Pulmonary artery hypertension is not likely [4].

The clinical features of pulmonary hypertension in HIV infection are not different from those of classic primary pulmonary hypertension.

We report a case of HIV infection associated with severe pulmonary arterial hypertension who presented to us with complaints of fever, cough, chest pain and progressive shortness of breath. On investigation, he was found to have HIV infection and severe pulmonary arterial hypertension. He was started

on anti-retroviral therapy along with sildenafil but he developed multiple complications and ultimately died of septic shock.

CASE REPORT

A 28 year old male taxi driver was admitted with high grade fever, orthopnea, and cough with mucoid expectoration, retrosternal chest pain and progressive shortness of breath for four months. On examination he was found to be thin build, febrile, there was icterus, palpable liver and crepitations in right axillary area of chest.

Investigations revealed Hb-12.7gm%, TLC-7000/cmm, platelet counts -1.80 lakhs, Serum bilirubin (Total/Direct)-1.4/1.0 mg/dl, malarial antigen, dengue serology and H1N1 antigen were negative. Chest x-ray showed non-homogenous opacity in right middle zone (Fig. 1). HRCT-chest showed right middle lobe pneumonia, cardiomegaly and pulmonary arterial dilatation (Fig. 2, 3).

Patient's 2-D echocardiography was consistent with severe pulmonary arterial hypertension (PASP- 90 mmHg) and RA/RV dysfunction. CT-pulmonary angiography ruled out pulmonary embolism. Ultrasonography of abdomen suggested minimal

ascites, congestive hepatomegaly, dilated inferior vena cava.

Other investigations done, showed ELISA for ANA doubtful positive, c-ANCA- positive, p-ANCA negative, Angiotensin-Converting enzyme (ACE) level normal. Viral hepatitis markers were non-reactive.



Fig. 1: Right middle zone ill-defined shadow



Fig. 2: CT-scan shows right middle lobe consolidation

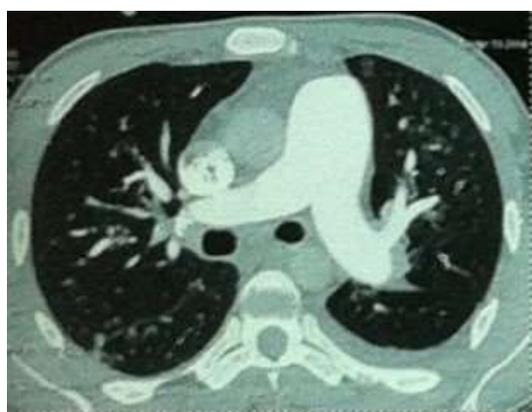


Fig. 3: CECT chest shows dilated PA trunk

Patient's sputum AFB stain was negative; blood culture showed no growth but urine culture grew E.coli. He was found to be HIV-1 reactive, confirmed by western blot, reactive antibodies were found against gp160, gp120, gp41, p55, p24, p2w7, p66, p51, p31. Absolute CD3 and CD4 counts were 1137 and 227 cells/mm³ respectively. HIV viral load was 5, 86,000 copies/ml.

Patient was started on antibiotics according to sensitivity, sildenafil, antiretroviral therapy [Efaviranez, Emtricitabine, and Tenofovir once a day fixed dose combination], PCP prophylaxis, low dose diuretic and oxygen therapy. During course of hospitalization of 4-5 weeks, his symptoms did not improve in spite of treatment. He started to complain of diarrhea, vomiting and bilateral lower limb pain with swelling. Venous Doppler of lower limb revealed DVT in left superficial femoral vein. Patient was started on low molecular weight heparin. Repeat investigations showed TLC (2700/mm³), thrombocytopenia, low albumin-1.9 gm/dl, increased serum alkaline phosphatase-1551U/L, raised serum bilirubin (Total) -1.9 mg/dl and raised SGOT/SGPT-158/63U/L. The CD4 counts improved to 341cells/mm³. Also the pneumonic patch regressed radiologically.

A repeat urine culture grew *Proteus mirabilis*, the antibiotics were modified accordingly. Patient's generalized weakness, breathlessness; nonproductive cough did not improve significantly. He had recurrent hypoglycemia and hypernatremia which were managed with 25% dextrose and extra salt supplementation. The patient then developed severe sepsis with shock from which he did not recover.

DISCUSSION

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by elevated pulmonary arterial pressures and pulmonary vascular resistance (PVR) leading to right ventricular failure and premature death [5]. Pulmonary arterial hypertension occurs with increased frequency among patients with human immunodeficiency virus (HIV) infection. With prolonged survival and improved control of infectious susceptibility, vascular complications have emerged as a significant source of morbidity and mortality in HIV-infected patients [6]. These vascular complications, affecting >10% of those with HIV infections including myocardial and pericardial tumours, cardiomyopathy, peripheral vasculitides, ischemic heart disease and pulmonary hypertension [6].

The first case of pulmonary hypertension associated with HIV infection was described by Kim and Factor in 1987 in a hemophiliac patient having membrane proliferative glomerulonephritis [7].

The prevalence was estimated to be approximately 0.5% in HIV-infected patients by Opravil *et al.* [1] in 1997, before the HAART era. According to Sitbon *et al.* [8] in 2008, the prevalence remained at 0.5% even in the modern era of HIV therapy. It has suggested that HAART has not made a dramatic impact on the prevention of HIV-related PAH. The incidence of HIV related PAH is found to be greater than that of primary pulmonary hypertension (PPH) in the general population [9].

The occurrence of HIV associated pulmonary arterial hypertension has been seen in younger population and reported interval between onset of symptoms and diagnosis is six months [10].

It has been suggested that the increased incidence of PAH in patients with HIV might be the result of an indirect role of the virus, stimulating the host to release proinflammatory cytokines or growth factors that would result in PAH [11-14].

Although HIV-related PAH is clinically and histologically similar to idiopathic pulmonary arterial hypertension (IPAH), the pathobiological mechanism leading to the development of PAH in patients with HIV infection remains unclear [15].

It was thought previously that there is direct role of viruses on endothelial cell injury but this was disproved by Mette *et al.* [16]. They were not able to identify either HIV-1 p24 antigen or the HIV gag RNA in pulmonary arteries of patients with HIV-associated pulmonary hypertension.

As a result of better prophylaxis against opportunistic infections and longer survival, noninfectious complications, such as lymphocytic interstitial pneumonia, non-Hodgkin's lymphoma, and pulmonary hypertension, are becoming more prominent [10, 17]. Pulmonary hypertension might be directly related to HIV infection [18, 19]. In a review of HIV-associated pulmonary hypertension by Mesa *et al.* [20] none of the 33 reported cases with known histology had pathologic evidence of foreign body granulomatosis.

Our patient was found c-ANCA positive which is a risk factor in genesis of portal hypertension, but in a study by Opravil *et al.* [1] found that an autoimmune phenomenon in the pathogenesis of HIV-associated pulmonary hypertension would be unlikely. The ANCA antibodies in this patient were false positive phenomena.

Survival of HIV-associated pulmonary hypertension patient has been worse, 51% as reported by Petitpretz *et al.* [21], than survival of patients with

Primary pulmonary hypertension as reported by National Institutes of Health registry for PPH.

Treatment of HIV associated PAH includes anticoagulants, vasodilators and highly active anti-retroviral therapy (HAART). One study of HIV positive patients treated with antiretroviral agents showed a decrease in the right atrioventricular pressure gradient vs a group of HIV patients who were not treated [1].

CONCLUSION

HIV infection is a rare etiology of pulmonary arterial hypertension and exact pathogenesis is ill-defined. HIV infection is an independent risk factor for the development of pulmonary hypertension. These patients have high mortality due to multiple factors. Interestingly our patient was also developed lower limb DVT probably due to decreased mobility and high preload caused by severe PAH. The appearance of unexplained cardiopulmonary symptoms in HIV-infected individuals should influence the clinician to work up for pulmonary hypertension. We conclude that search for non-infectious causes of dyspnea in HIV infected patients is very important and conversely every patient of primary pulmonary hypertension must be tested for HIV infection

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