Case Report

Integrative Pulmonary Medicine

A Case of Deep Vein Thrombosis, Pulmonary Hypertension with Retro-Viral Disease

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Abstract

Human Immune Deficiency Virus (HIV) infection is known to induce Pulmonary Arterial Hypertension (PAH) and Venous Thrombo Embolism (VTE). This is the case report of a 50-year old man being treated with Highly Active Anti-Retro Viral Therapy (HAART) for 8-9 years. He was admitted, evaluated, investigated and treated with a combination antibiotic for respiratory infection, a diuretic for treating oedema and an oral anticoagulant for treating VTE. The symptoms appear to be chronic complications of progression of retro-viral disease. The case is from a tertiary care hospital in western India (Maharashtra).

Keywords: Pulmonary arterial hypertension (PAH), Deep vein thrombosis (DVT), Pulmonary embolism (PE), Human immunodeficiency virus (HIV)

Introduction

Human Immune Deficiency Virus (HIV) is one of the known independent risk factors for PAH and VTE. Many factors have been identified to be responsible for this. The pulmonary vasculature is a delicate microenvironment susceptible to various complex pathogenic events. The factors like concentric laminar intimal fibrosis, medial hypertrophy, recanalised thrombi and plexiform lesions may trigger PAH. In addition influence of HIV infection on clotting factors, adhesiveness of endothelium, platelet hyper-activation and induction of other pro-inflammatory factors may induce VTE.

Morbidity with retro-viral disease is known. The patient (VM, 50), a known case of retro-viral disease was on anti-retroviral combination drug LNZ (Lamivudine 300 mg + Nevirapine 200 mg + Zidovudine 600 mg).

He is a borderline case of hypertension being treated with a diuretic (Fruresamide 40 mg + Spironolactone 25 mg).

Two years ago, he developed deep vein thrombosis along with multiple pulmonary emboli.

This case report is the first from our centre to increase awareness on existence of PAH and VTE along with HIV infection. Although introduction of HAART has increased longevity in patients of HIV, attention on additional complications like PAH and VTE and its relation to HIV is of clinical interest.

Case Report

The chronology of the case is as follows

A 50 year male (VM) is a known case of Retro-Viral Disease (RVD) for last 8-9 years and was taking an anti-retroviral combination drug LNZ (Lamivudine 300 mg + Nevirapine 200 mg + Zidovudine 600 mg).
exertion, abdominal pain and anorexia. He gets dyspnoea even on walking 100-200 feet.

On admission, his BP was 140/80 mm of Hg, pulse rate of 120/min, respiration rate was 25/min and CD count was found to be 564 cells/mm³. There was no oedema in leg and other systems were normal. Right Ventricular Systemic Pressure (RVSP) was found to be 70 mm of Hg indicating pulmonary hypertension.

His chest X-ray showed blunting of right Cardio Phrenic (CP) angle and mild cardiomegaly, probably due to prolonged High Blood Pressure (HBP), chronic pulmonary embolism and pulmonary hypertension. ECG showed right ventricular hypertrophy with strain. Ultrasonography of chest showed loculated pleural effusion at right CP angle without pericardial effusion. Echocardiography showed dilated right atrium and right ventricle. There was mild left ventricular hypertrophy and mild systolic dysfunction. The diagnosis of chest infection causing pneumonia was based on chest X-ray and ultrasonography of chest. Cardiac complications were diagnosed on the basis of observations of ECG and echocardiography. The diagnosis was mild heart failure due to chest infection, multiple pulmonary emboli causing pulmonary hypertension and retroviral disease.

The patient was treated with an antibiotic (Amoxycillin 500 mg+ Clavulanic acid 125 mg). Antiretroviral Therapy (ART) was used as a combination drug LNZ (Lamivudine 300 mg + Nevirapine 200 mg + Zidovudine 600 mg) and a diuretic for treating blood pressure with composition of (Frusemide 40 mg + Spironolactone 25 mg). For treating pulmonary embolism, oral Acenocoumarol 2mg was used.

Discussion

Pulmonary Arterial Hypertension (PAH) is a progressive disease caused by chronic obstruction of small pulmonary arteries, leading to right ventricular failure and potential death. It appears to be causally related to HIV-infection.

The first case of HIV-related PAH was described in 1987 [1]. Subsequently, several other cases have been reported [2-10]. A review of 131 cases of HIV-related PAH indicated shortness of breath, pedal oedema, cough, fatigue, and syncope and chest pain as common presenting signs. Right ventricular hypertrophy was the most common finding and right cardiac dilation was the most frequent observation on ECG [7]. It is consistent with observations in present case. A study of 18 cases of PAH in HIV infection indicated the elapse time between HIV infections and PAH diagnosis was 12.2 +/- 6.9 years. Highly Active Anti-Retroviral Therapy (HAART) was associated with accelerated onset of PAH. Survival rates were 93.8%, 92.9% and 85.7% at 1, 2 and 3 years respectively. It was concluded that survival rates of HIV related PAH patients were higher due to aggressive therapy [10]; these observations are relevant in the present case.

Earlier, HIV-related PAH was estimated to have a rate of 0.5% in developed countries [2,11]. It is argued that the incidence of PAH in patients of HIV increased to almost 25-fold as compared to incidence of PAH in general population [12]. Higher incidence of PAH has been indicted in HIV patients in a number of cohort studies [13-16]. Epidemiological investigations also point out higher incidence of PAH in HIV patients [17-28].

Pathogenesis of HIV-related PAH has been discussed [28,29]. The pulmonary vasculature is a delicate micro-environment susceptible to various complex pathogenic events. The events may trigger PAH. Histologically, lesions in HIV-infected patients with PAH are similar to their uninfected counter-parts. These features include concentric laminar intimal fibrosis, medial hypertrophy, recanalised thrombi and plexiform lesions [12]. It seems HIV induced chronic inflammation and immune hyperactivation may promote inflammatory environment. Viral proteins like Nef and Tat have been shown to lead to endothelial dysfunction and increased inflammation through cytokines, independent of virus production [28,29]. It appears that in present case, chronic existence of HIV has promoted thromboembolism initially followed by PAH later.

Following causes of HIV-related PAH have been indicated [29].

Certain
- Genetic predisposition
- Thrombosis & chronic thromboembolic pulmonary hypertension
- HIV-related proteins
- HIV-related inflammation

Probable
- Intravenous drug use
- Co-infections
- Left-sided heart disease

Prognostic factors for survival of patients with HIV-related PAH have been investigated. Greater functional
class at the time of diagnosis is associated with a poorer survivor [29]. It is also observed in one of the Indian study [30] that early detection of PAH in HIV patients is essential and prompt institution of HAART should be considered. It is further indicated that better results are observed if the therapy is started at earlier stage. The classification of PAH in present case matches with Group 4 of ESC/ERS guidelines [31] CD4 cell count of >212 cells/mm$^3$ is associated with a better prognosis [29]. In the present case, CD4 count was observed to be 564 cells/mm$^3$. It indicates better prognosis.

In the present case, Deep Vein Thrombosis (DVT) has been observed during last two years. Existence of venous thromboembolism in patients of HIV has been reported [32-34]. HIV infection has been recognized as a prothrombotic condition and has shown a frequency of HIV-infected patients ranging from 0.19-7.63% per year [35]. Several epidemiological studies have reported on the occurrence of VTE among HIV-infected patients [32-47]. It appears that chronic HIV infection is associated with two to ten-fold increase risk of venous thrombosis in comparison with a general population [46]. Some of the risk factors are low CD4 cell count, deficiency of protein S or C. Other risk factors are protease inhibitor therapy, presence of active opportunistic infections, anti-phospholipid antibodies including anti-cardiolipin antibodies and lupus anti-coagulant [35]. Use of oral anticoagulants or low molecular weight heparin is suggested. It is further suggested that pulmonary embolism should be included in the differential diagnosis when patients with HIV/AIDS have unexplained dyspnea or hypoxaemia [35]. These arguments are relevant in the present case because the patient has shown pulmonary embolism as well as deep vein thrombosis. Thus appearance of PAH and VTE seems to be causally related to HIV infection, probably through immunological defence mechanisms.

Following multifactorial aetiology of HIV-related venous thromboembolism has been indicated [35]

- HIV-related malignancies
- Endothelial dysfunctions
- HIV-related hypercoagulable state
- Genetic risk factors
- Viral risk factors
- Acquired traditional risk factors
- Opportunistic infections
- Iatrogenic factors

Interested readers are advised to see a diagram [35] summarizing pathogenesis of HIV-related VTE.

HAART is the principle treatment for treating HIV. There are reports of use of antiretroviral therapy in treating patients of PAH with HIV [16,48-50]. The regimen of HAART in the present case does not contain protease inhibitors; it contains two nucleoside-reverse-transcriptase inhibitors (Lamivudine and Zidovudine) and one non-nucleoside-reverse transcriptase inhibitor (Nevirapine). Out of these drugs, only Nevirapine has been shown to be mild to moderate inducer of CYP3A4 and CYP2B6. Protease inhibitors are known to be CYP450 isoenzymes; but they are absent in the antiretroviral drug combination given to the patient. HIV itself is related to hypercoagulable state; hence the complication of VET appears to be related to long-standing HIV itself. Contribution of enzyme induction, if any, looks to be minimal. In addition, CD4 count in the present case is 564 cells/mm$^3$, which being higher than 200 makes relatively better prognosis.

A case report on HIV infection associated with DVT and venous ulcer is relevant to the present case [51].

**Conclusion**

A case of HIV-related PAH and VTE has been described. Higher incidence of PAH and VTE in a patient of HIV (10 to 25 times) is emphasized.

**Conflict of interest**

The authors declare that there are no conflicts of interest including financial, consultant, institutional and other relationships that might lead to bias or to a conflict of interest.

**References**


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