

CASE REPORT

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Epigastric pain as the initial presentation of undiagnosed HIV and its associated pulmonary arterial hypertension

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ABSTRACT

Introduction: Due to increase in survival of HIV positive patients on antiretroviral therapies, longer term complications of HIV infection have started to surface including HIV related pulmonary arterial hypertension (HIV-PAH). In the 1990's the occurrence of HIV-PAH was estimated to be at 0.5% (1:1200) in HIV positive patients which is 2500 times higher than in the general population (1-2:1,000,000) and seems to remain at the same level despite advances in diagnosis and treatment. **Case Report:** A case of a 28-year-old African-American female presenting with abdominal pain, increased abdominal girth, weight gain, and lower extremity swelling of one week duration is presented. She was not previously diagnosed with HIV. Upon admission she was diagnosed with HIV related pulmonary arterial hypertension World Health Organization functional class III. **Conclusion:** What makes our case unique, is the rarity of the disease entity, unique gastro intestinal presentation, young age and newly diagnosed HIV and associated pulmonary arterial hypertension. The presence of epigastric pain and increased abdominal girth should increase the suspicion of PAH with right heart failure.

Keywords: HIV, Pulmonary hypertension, Epigastric pain

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INTRODUCTION

Due to the increase in survival of HIV positive patients on antiretroviral therapies, non-infectious complications associated with HIV infections are becoming more common including HIV related pulmonary arterial hypertension (HIV-PAH). In 1987, Kim et al. described the first case of HIV with pulmonary artery hypertension (PAH) [1]. At the time, PAH was not known to be directly linked to HIV. It is not yet known how HIV directly causes PAH.

Pulmonary arterial hypertension is a diverse group of conditions that lead to elevated pulmonary pressures. PAH is diagnosed when the pulmonary arterial pressure and pulmonary vascular resistance are elevated in conjunction with a normal pulmonary capillary wedge pressure [2]. Hemodynamically, it is defined as an increase in the mean pulmonary arterial pressure to 25 mm Hg at rest or 30 mm Hg during exercise [3].

In both HIV-1 and HIV-2 there is no apparent correlation between the severity of PAH and the stage of HIV infection, the degree of immunodeficiency, or CD4 T-lymphocyte counts [4, 5]. Although it is likely that PAH-HIV has an underlying etiology specifically related to HIV infection, it shares several key clinical and pathological similarities with other forms of PAH.

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Idiopathic PAH and HIV-PAH share the same histopathological findings including medial hypertrophy, intimal thickening with or without plexiform lesions (89%), veno-occlusive disease (7%), and thrombotic pulmonary arteriopathy in 4% of cases [4].

Patients with HIV-PAH tend to present at a younger age [5, 6] and the major presenting symptom of HIV-PAH arise secondary due to right ventricular dysfunction. In the 1990's the occurrence of HIV-PAH was found to be 1:1200 which was 2500 times higher than in the general population which was 1:1,000,000 [7–10]. Presenting symptoms in patients with HIV-PAH are shortness of breath (85%), lower extremity edema (30%), non-productive cough (19%), fatigue (13%), syncope (12%), and chest pain (7%) [4]. PAH can be caused by idiopathic causes, familial autosomal dominant type, congenital heart disease or HIV infection.

Prognosis is dismal for patients in World Health Organization (WHO) or New York Heart Association (NYHA) functional class III-IV, with a three year survival rate of only 28% [5]. Factors associated with better survival in NYHA functional class III-IV include CD4 cell counts greater than 212 cells/ μ l at diagnosis, treatment with HAART and treatment with IV epoprostenol. Only the CD4 count remained significant on multivariate analysis [5]. Asymptomatic HIV-PAH patients were found to be younger (38 ± 3.6 vs 41 ± 6.6 years) and had significantly lower HIV viremia (1038 ± 909 vs 54726 ± 45339 copies/ml) than symptomatic HIV associated PAH patients [11].

PAH may not become clinically evident until severity increases consequently delaying the diagnosis of the disease until very late stages (NYHA FC III or IV). Approximately two thirds of deaths in HIV-PAH are attributed to the direct consequence of PAH, including right sided heart failure, cardiogenic shock and sudden cardiac death [4]. The time interval between the onset of symptoms and the establishment of diagnosis of PAH was shorter in patients with HIV-PAH than primary PAH alone. The mean length of time from symptoms to diagnosis of HIV-PAH was about six months compared to primary PAH alone which is 2.5 years [12, 13]. Keeping a low threshold for the diagnosis of PAH in patients presenting with HIV and shortness of breath can help with early treatment and improving survival in these patients.

CASE REPORT

We are presenting the case of a 28-year-old African-American female presenting with epigastric pain and increased abdominal girth with lower extremity swelling of one week duration. She had significant weight gain of 15 pounds over the past one month, orthopnea and had difficulty performing activities of daily living. Abdominal pain was localized to the epigastum and was unrelated to food intake. The pain had no known exacerbating or relieving factors. She denied fever,

chills, chest pain, nausea and diarrhea. She had shortness of breath with mild exertion and a chronic non-productive cough of a few months duration. She was incarcerated in prison two years ago where she was found to be HIV positive. She had a history of crack cocaine use and denied any pertinent family or promiscuous sexual history. She did not smoke or abuse alcohol. She had no known drug allergies and was not taking medications at time of admission.

Vitals signs were temperature 35.6°C , BP 115/91, mmHg, heart rate 73/min, respiratory rate 22/min, and pO_2 95% on two liters of oxygen. On physical examination. She had positive JVP up to the ear lobes bilaterally. Cardiovascular exam showed a regular heart rate, with a loud P2 heard over left upper sternal border. Her point of maximal impulse was inferolaterally displaced. On pulmonary exam she had bibasilar crackles. On abdominal exam she had a positive hepatojugular reflex. The abdomen was distended and diffusely tender over the epigastric region and right upper quadrant (RUQ) with no rebound or peritoneal signs. She had lower extremity pitting edema (3+). She also had a positive macular erythematous skin rash over shins of her bilateral lower extremities.

Labs on admission showed Na 133 mEq/l (135–147 mEq/l), K 3.5 mEq/l (3.5–5.2 mEq/l), Cl 100 mEq/l (95–107 mEq/l), CO_2 23 mmHg (19–25 mmHg), BUN 26 mg/l (7–20 mg/l), and Cr was 1.8 $\mu\text{g/l}$ (0.5–1.4 $\mu\text{g/l}$), Alk P was 80 U/L (33–131 U/L), SGPT 90 IU/L (<35 IU/L), SGOT 129 IU/L (<35 IU/L), Amylase 85 U/L (70–200 U/L), lipase 36 U/L (7–58 U/L), troponin <0.10 ng/mL (<0.10 ng/mL), BNP was 1893 pg/ml (<200 pg/ml), and TSH was 3.95 mIU/ml (0.25–4.3 mIU/ml), Hb 11.5 g/dl (12–15 g/dl), Hct 35% (36–44) MCV 82 fl (80–100fl), WBC 4.6×10^3 ($4.5\text{--}10 \times 10^3/\text{mm}^3$), platelets 189×10^3 ($100\text{--}450 \times 10^3$), INR was 1.09 (1.0). Ultrasensitive viral load was 12,900 copies/ml with a log of 4.11 copies/ml. CD4 count was 292 cells/ μ l with 10.49. CD4 out of total T cells. Arterial blood gases on room air showed pH 7.44 mmHg (7.35–7.45 mmHg), pCO_2 36 mmHg (35–45 mmHg), pO_2 of 66 mmHg (70–100 mmHg), and an A-a gradient of 37.5 mmHg (5–10 mmHg).

Urine drug screen was negative, and had 200 mg/dl of protein on spot testing. In a 24 hr urine collection 3.1 g of protein was recorded. Urine analysis showed normal results except for trace leukoesterase and rare white cells.

Skin rash was biopsied and showed HIV related prurigo nodularis. Ultrasound of the abdomen showed hepatomegally with normal liver architecture. No ascites was found. CT of the abdomen showed a small left pleural effusion, cardiomegally, small pericardial effusion and abdominal and pelvic ascites. Chest X-ray showed no plural effusion with no infiltrates in the lungs. She had prominent intersistial markings within the perihilar region. V/Q scan was done secondary to renal failure and showed low probability for P/E. ECG showed normal sinus rhythm, RVH, and p-pulmonale. Transthoracic echocardiogram showed right ventricular dilation and right ventricular hypokineses with a septum

bulging into the left ventricle. Ejection fraction was 55%, no LVH, grade 1 diastolic dysfunction with a grade II tricuspid regurgitation. Right heart catheterization showed pulmonary artery (PA) diastolic pressure was 53 mmHg, PA systolic was 98 mmHg, the PA mean was 66 mmHg, the pulmonary capillary wedge pressure was 10 mmHg, RV systolic pressure was 98 mmHg, cardiac output was 2.2 L/min and RA wedge pressure was 16 mmHg.

A six minute walk test showed: SpO₂ 95% at room air and a heart rate of 89/min. After walking a distance of 600 feet her spO₂ dropped to 92% and her heart rate increased to 95 min. She was assessed to be at WHO FC III.

DISCUSSION

Three major European studies, The Swiss HIV Cohort study, a prospective French National Study, and an Italian registry study have been investigating the prevalence of PAH in the HIV infected population in more recent years. In the Swiss study, 13,400 patients (by 2006) were enrolled in the study, and only 66 cases of PAH were observed (0.5%) [9], compared to the French study of 7648 patients, of whom 5 had confirmed PAH (0.46%) [10], and the Italian study of 5000 HIV patients of whom only 11 had PAH (0.2%) [11]. In the Swiss study, 24 were diagnosed with PAH most of whom, were on HAART therapy for more than a year, suggesting the drug therapy itself does not protect against the development of PAH [14]. On the other hand, the Italian study started in 2004, claims to have a lower diagnosis rate attributed to a higher level of HAART therapy prior to diagnosis [11].

Our patient presented with symptoms that are very unique and to our knowledge have not been mentioned previously. She presented with epigastric pain and increased abdominal girth, signifying advanced disease in a previously undiagnosed patient.

According to the results in the French National screening algorithm a trans-thoracic doppler echocardiogram and right catheterization are most applicable in routine clinical practice [10]. Our patient presented with 98 mmHg at rest which is equivalent to the highest documented finding in the Swiss study. PAH patients usually have normal pulmonary capillary wedge pressure (<15 mmHg) excluding pulmonary hypertension secondary to left-sided heart disease and a PVR of more than 3 Wood units by continuous wave doppler echocardiogram [15]. In the Swiss study, the median pressure gradient measured in the patients was found to be between 43–80 mmHg in patients on HAART and 52–100 in patients not controlled on HAART [9].

In order to correctly diagnose PAH, the presence of pulmonary embolism needs to be excluded by lung perfusion scan or CT angiography. There needs to be a normal left ventricular function, with no evidence of congenital or valvular heart disease. Chronic obstructive pulmonary disease, and history of IV drug use need to

be ruled out as well. Physical exam findings include a loud P₂, a right sided S₃ gallop, a murmur of tricuspid regurgitation and increased jugular venous pressure with peripheral edema [4]. Positive changes are commonly seen on ECG (79%) and chest X-ray (74%) [7]. ECG signs include non specific signs of RVH, right atrial abnormalities and right axis deviation with sinus tachycardia [4, 7]. Transthoracic echocardiography may show a range of abnormalities including right heart enlargement, tricuspid regurgitation, and paradoxical septal motion abnormalities [16].

The current accepted algorithm for diagnosis of PAH includes, first, treating symptoms and stabilizing the patient with oxygen, diuretics, and anticoagulants. There is little indication for calcium antagonists due to the high side effects associated and the rarity of vasodilator response (10%) and the poor response rates (50%) in HIV-PAH patients [17]. Phosphodiesterase 5 inhibitor sildenafil and subcutaneous and IV injection of prostacyclin analogue treprostinil are currently the only approved treatments for patients with NYHA FC II patients. The endothelin receptor antagonist Bosentan and sildenafil are the first line therapies of choice for WHO class III patient. For patients who have more severe PAH with WHO FC IV, epoprostenol is recommended [17, 18]. The potential for drug interactions between PAH therapies and some HAART, may require a little closer monitoring and adjustments of medications in HIV-PAH. Treatment with the oral dual ERA bosentan has been shown to delay clinical worsening without adversely affecting the control of HIV infection, and without significant interaction with HAART [18, 19]. The role of HAART remains to be controversial in controlling or reversing HIV-PAH [5]. If most of these treatments and combination treatments fail, a heart- lung transplant may be the only other option.

Our 28-year-old patient presented with a CD4 count of 293 and viral load of 12900 copies per ml, was diagnosed with a WHO FC III predicting a dismal prognosis. Until the late 1990's, the median survival time from diagnosis of PAH was 2.8 years, and more specifically six months for NYHA class IV, due to the lack of specific treatments [20]. Over the last decade more specific treatments have been developed targeting the main pathways for development of PAH. Prostanoids, nitric oxide, phosphodiesterase type 5 inhibitors and endothelin receptor antagonists have been developed to target the abnormalities in structure and function of endothelium and smooth muscle cells in the pulmonary vasculature [21].

CONCLUSION

What makes our case unique, is the young age, the rarity of the disease entity, and the unique gastrointestinal presentation. The presence of epigastric pain and worsening abdominal girth in an HIV patient should raise the suspicion of PAH with secondary right heart failure. Patients with PAH are routinely checked

for HIV, but the opposite is rarely done. Patients with HIV may routinely need to be checked for PAH and an echocardiogram should be done to get baseline values if PAH is not yet present or suspected. Infectious causes are not always the cause of shortness of breath in HIV positive patients and PAH should be included in the differential.

Author Contributions

Yousef Usta – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Akram Ibrahim – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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