Cor Pulmonale from Concomitant Human Immunodeficiency Virus Infection and Methamphetamine Use

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INTRODUCTION

Patients with human immunodeficiency virus (HIV) have 1,000 times the risk of developing pulmonary artery (PA) hypertension (PAH) as non-HIV-infected individuals, but PA pressures (PAPs) rarely reach systemic levels. At the same time, PAH associated with methamphetamine use is associated with a grave prognosis and higher mortality than idiopathic PAH (IPAH). This case report demonstrates the particularly pernicious and synergistic effect of HIV infection and long-term recreational methamphetamine use in the development of very severe PAH and cor pulmonale. Multimodality imaging and hemodynamic studies in our patient revealed PAPs and cardiac remodeling well beyond what is typically seen in non–methamphetamine users with HIV-associated PAH.

CASE PRESENTATION

A 41-year-old man presented to the emergency department (ED) with chest pain and dyspnea. The patient—who had a long history of polysubstance use disorder, including smoking methamphetamine daily—was diagnosed with HIV infection 10 years earlier but refused any HIV-related care at that time. Four years before the current presentation, evaluation for progressive exertional dyspnea revealed PAH, and medical therapy was initiated. Although his viral load was very high (>25,000 copies/mL), he continued to decline HIV treatment. Eighteen months later, however, he established care with an HIV physician and began highly active antiretroviral therapy (HAART).

Five months prior to the current presentation—when his exercise tolerance was severely limited (World Health Organization symptom class III)—he underwent right heart catheterization that confirmed profound pulmonary hypertension unrelated to left heart disease (Table 1). Three weeks before presenting to our ED, he discontinued his PAH medications (ambrisentan, selexipag, and riociguat) because of nausea and vomiting.

He presented to our ED complaining of left-sided chest pain radiating to his back that had begun after an argument with his partner. He reported last smoking methamphetamine earlier that day. He was afebrile and normotensive and had a normal heart rate and a room air oxygen saturation (SpO_2) of 92%. His complete blood count and comprehensive metabolic panel were within normal limits. His CD4 count was 418 cells/μL (normal reference range, 359-1,439 cells/μL).

Computed tomography (CT) angiography of the chest revealed severe right heart enlargement, marked dilation of the main PA consistent with marked chronic pulmonary hypertension (Figure 1), and reflux of contrast into the hepatic veins consistent with elevated right atrial (RA) pressure (Figure 2).

Transthoracic echocardiography (TTE) provided complete hemodynamic assessment of right and left heart filling pressures (Figure 3). There was severe pulmonary hypertension with an estimated PA systolic pressure (PASP) of at least 115 mm Hg, a PA diastolic pressure (PADP) of at least 23 mm Hg, and a mean PAP (MPAP) of at least 45 mm Hg. The right ventricle (RV) was hypertrophied, severely dilated, and severely hypokinetic. The RA was dilated. The inferior vena cava (IVC) was also dilated (end-expiratory diameter 2.2 cm with <50% collapse with inspiration), corresponding to an estimated RA pressure of 15 mm Hg. There was also paradoxical interventricular septal motion due to RV pressure overload (Figure 4; Video 1) as well as moderate tricuspid and mild pulmonic regurgitation (Video 2). There was no pulmonic stenosis. Otherwise, LV wall motion and ejection fraction were normal. Left heart diastolic

Table 1 Right heart catheterization from 5 months prior to presentation

Systolic blood pressure	124 mm Hg
Diastolic blood pressure	68 mm Hg
Aortic Saturation, %	93
RA	7 mm Hg
RVSP	98 mm Hg
RV diastolic pressure	10 mm Hg
PASP	95 mm Hg
PADP	32 mm Hg
MPAP	62 mm Hg
PCWP	8 mm Hg
Cardiac Output (Fick)	3.0 L/min
Cardiac Index (Fick)	1.8 L/min/m^2
Pulmonary Vascular Resistance	18 Woods
Pulmonary Vascular Resistance index	30 Woods · m^2
Body surface area	1.7 m^2

function was preserved with normal left atrial pressure. There was no significant pericardial effusion.

During the admission, ambrisentan was restarted and treatment with tadalafil was initiated. The patient continues to be medically managed and is followed in the pulmonary hypertension clinic.

DISCUSSION

While all PAH patients have remodeling of the pulmonary arterial system that can progress to a pressure-overloaded right heart, the under-
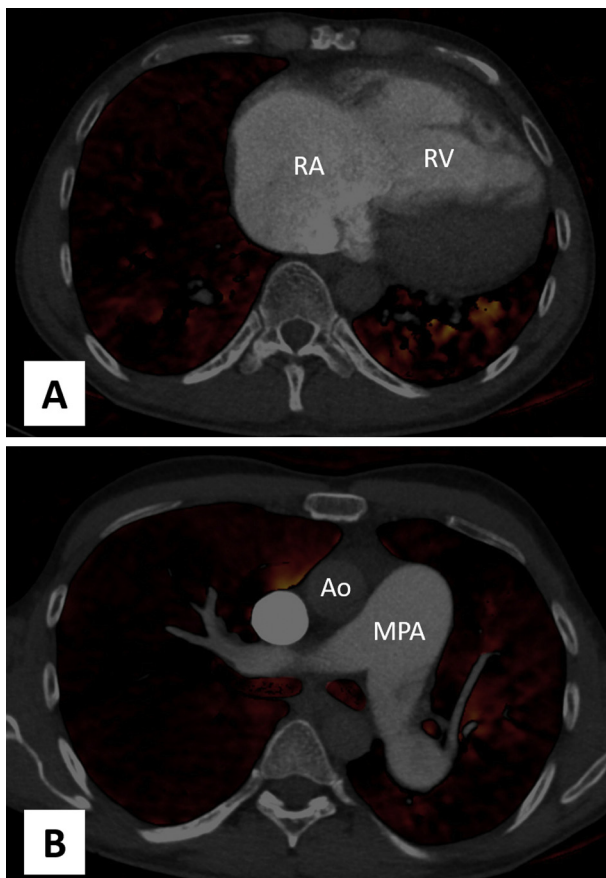

Figure 1 Perfused blood volume image from a dual energy CT pulmonary angiogram demonstrates a markedly dilated right atrium (RA) and dilated and hypertrophied RV **(A)** and a markedly dilated main PA (MPA) **(B)**, consistent with chronic severe pulmonary arterial hypertension. *Ao,* Ascending aorta.
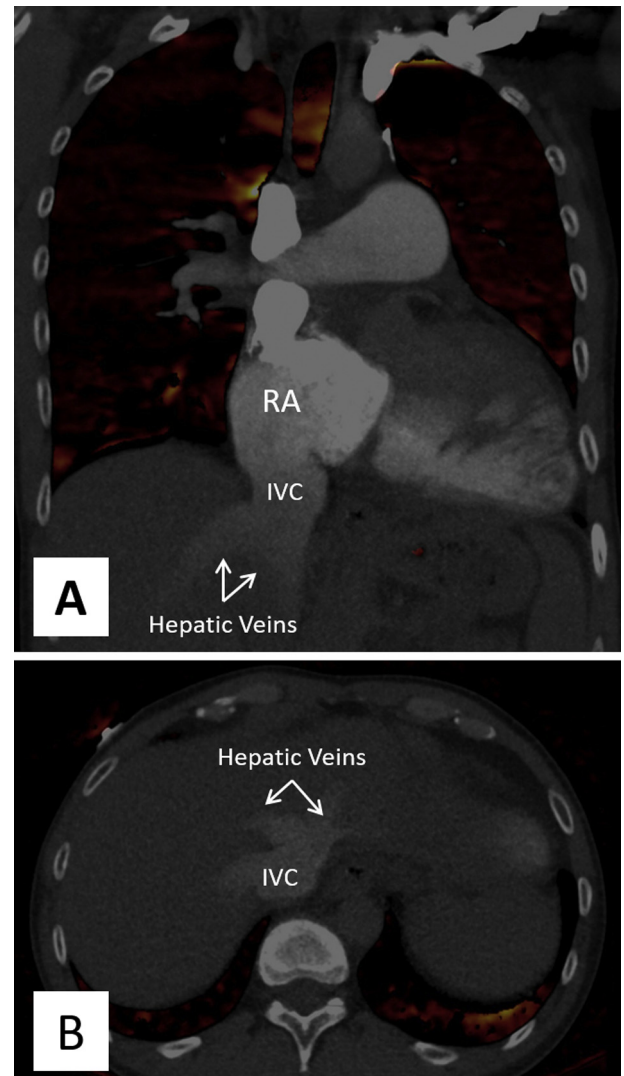

Figure 2 Perfused blood volume image from a dual energy CT pulmonary angiogram demonstrates a markedly dilated IVC **(A)** with contrast reflux into the hepatic veins **(B)** indicative of elevated RA pressures.

lying pathophysiology of PAH varies greatly. Epidemiologic studies have found that 39%-61% of PAH patients are considered IPAH, with the remainder attributed to a single specific risk factor.[1] Our case is noteworthy because the patient's profound PAH and consequent right heart failure were likely due to the combined effects of HIV and frequent amphetamine use—two known causes of PAH development, each associated with a generally poor prognosis.

Our patient's HIV was untreated prior to his PAH diagnosis, which likely contributed to his severe disease presentation and rapid progression. Patients with HIV infections have a 1,000-fold lifetime risk of developing PAH compared to the general population.[2,3] Among all HIV patients, approximately 0.5%-10% develop PAH during their lifetime.[2,3] In the era of HAART and aggressive use of prophylactic antibiotics, this number is expected to continue to rise as patients die less frequently of opportunistic infections and live longer to encounter conditions associated with chronic HIV infection.[2,3] HIV-associated
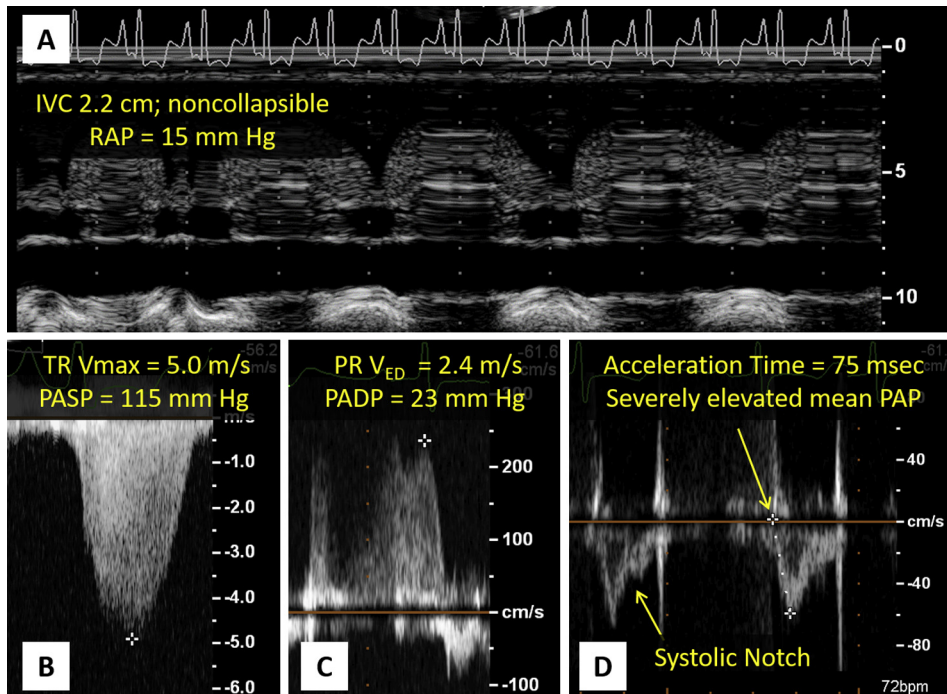
Figure 3 Transthoracic echocardiography spectral Doppler demonstrates complete hemodynamic assessment of right-sided pressures including the RA pressure **(A)**, PASP **(B)**, PADP **(C)**, and MPAP **(D)**. Note the rapid acceleration time and systolic notching in the right ventricular outflow tract spectral Doppler tracings indicative of markedly elevated mean and peak systolic PAPs, respectively.
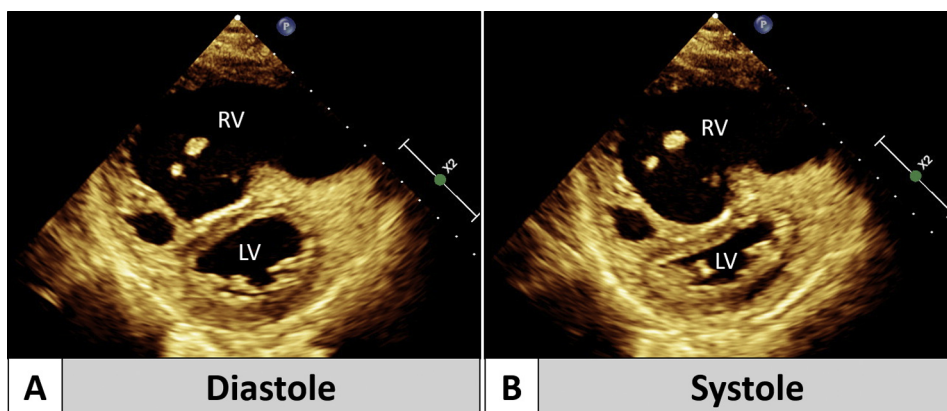

Figure 4 Transthoracic echocardiography imaging at the midpapillary short-axis level in diastole **(A)** and systole **(B)** demonstrates marked paradoxical interventricular septal motion indicative of a markedly elevated right ventricular (RV) systolic pressure. Video 1 corresponds to this figure.

PAH (HIV-PAH) is thought to develop as a result of the chronic inflammatory state associated with the viral infection. In particular, proinflammatory cytokine cascades are upregulated in HIV infections, stimulating vascular smooth muscle proliferation.[2] Studies have shown that HAART delays the onset of HIV-PAH and increases survival among HIV-PAH patients with high CD4 counts and low viral loads.[4] In our case, the patient went without HAART for over a decade.

Echocardiography allows for complete hemodynamic assessment of right heart anatomy, function, and pressures with some limitations. The RA pressure (RAP) can be estimated from the size of the end-expiratory diameter of IVC and the degree of IVC collapse during inspiration as recommended by the American Society of Echocardiography guidelines.[5] In the presence of severe tricuspid regurgitation (TR), this method may underestimated the RAP.

Peak RV systolic pressure (RVSP) can be estimated from TR spectral Doppler tracings using the simplified Bernoulli equation $RVSP = 4 * V_{TR}^2 + RAP$, where V_{TR} = peak TR jet velocity. In the absence of pulmonic stenosis (as was the case with our patient), peak PASP is practically the same as RVSP.[6] Similarly, the PADP can be estimated from the end-diastolic velocity of the pulmonic regurgitant (PR) jet: $PADP = 4 * V_{PR} + RAP$.[7] Mean PAP can be from the acceleration time (AT) of the right ventricular outflow tract pulsed-wave systolic velocity profile using the Mahan equation:

$MPAP = 79 * 0.46 * AT$.[8] This is especially helpful when no significant TR or PR jet is present.

HIV-PAH patients have been shown, by echocardiography, to have higher PAPs than non-HIV PAH patients. In one study, mean PASP was 5.1 mm Hg higher than in case-matched non-HIV patients.[9] But even compared to other HIV-PAH patients, our patient's PAPs were exceedingly high. In a 2008 study of a large cohort of HIV patients, those with known HIV-PAH had an MPAP of 46 mm Hg,[10] and other studies have classified PAH as "severe" with a PASP of greater than 65 mm Hg by TTE.[11] Our patient's MPAP was once measured to be as high as 74 mm Hg and his PASP as high as 132 mm Hg.

These high PAPs that are way beyond what is typically seen in HIV-PAH are likely accounted for by his long-term and frequent methamphetamine use. In a 2006 study, stimulant use (cocaine, amphetamine, or methamphetamine) was found in 28.9% of patients who were previously diagnosed with IPAH.[12] Although the precise pathophysiology of methamphetamine-associated PAH (Meth-PAH) is unknown, increased levels of circulating serotonin are thought to directly promote pulmonary smooth muscle proliferation and to increase reactive oxygen species that damage pulmonary endothelium.[13] In a 2018 prospective study comparing Meth-PAH patients with IPAH patients, Meth-PAH was associated with more severe RV dilation, more severe RV dysfunction, and more frequent RA dilation.[14]

Frequent methamphetamine also portends a poor prognosis. Only 47.2% of patients diagnosed with Meth-PAH survive to 5 years compared to 65.5% with IPAH; 10-year survival for Meth-PAH is 25% compared to 45.7% for IPAH.[14] Meth-PAH patients appear not to respond to nitric oxide challenges, suggesting a diminished effect of the therapeutic agents commonly used for PAH.[14] Our patient's echocardiographic findings also predict a shorter survival. Both RA enlargement and RV dysfunction are associated with more severe PAH and are predictors of increased mortality.[15] Moreover, paradoxical septal wall motion has a hazard ratio for death or transplantation of 1.45 (95% CI, 1.12-1.86).[15]

CONCLUSION

Our case demonstrates the synergistic effect of HIV infection and long-term methamphetamine use in the development of severe, life-threatening PAH and cor pulmonale.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2021.03.006.

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